IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ALCON MANUFACTURING, LTD., ALCON LABORATORIES, INC., and KYOWA HAKKO KOGYO CO. LTD.,	)	
Plaintiffs,	)	
v.	)	C. A. No. _____
BARR LABORATORIES, INC.,	)	
Defendant.	)	

COMPLAINT

Alcon Manufacturing, Ltd., Alcon Laboratories, Inc., and Kyowa Hakko Kogyo Co. Ltd. (collectively "Plaintiffs"), by their attorneys, for their Complaint, allege as follows:

1. This is an action for patent infringement under the patent laws of the United States, Title 35, United States Code, that arises out of the filing by Defendant Barr Laboratories, Inc. ("Barr") of an Abbreviated New Drug Application ("ANDA") with the U.S. Food and Drug Administration ("FDA") seeking approval to manufacture and sell a generic version of Patanol® ophthalmic solution, a drug product containing olopatadine hydrochloride, prior to the expiration of U.S. Patent Nos. 5,641,805 and 5,116,863.

PARTIES

2. Plaintiff Alcon Manufacturing, Ltd. is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 6201 South Freeway, Fort Worth, Texas 76134.

3. Plaintiff Alcon Laboratories, Inc. is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 6201 South

Freeway, Fort Worth, Texas 76134.

4. Plaintiff Kyowa Hakko Kogyo Co. Ltd. ("Kyowa") is a corporation organized and existing under the laws of Japan, having its principal place of business at 1-6-1 Otemachi, Chiyoda-ku, Tokyo 100-8185, Japan.

5. Upon information and belief, Defendant Barr is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 400 Chestnut Ridge Road, Woodcliff Lake, NJ 07677.

JURISDICTION AND VENUE

6. Jurisdiction and venue are proper in this district pursuant to 28 U.S.C. §§ 1331, 1338(a), 1391, and 1400(b).

7. Upon information and belief, Barr is in the business of marketing pharmaceutical products, which it distributes and sells throughout the United States, including the State of Delaware and the District of Delaware.

COUNT I

(Patent Infringement - 5,641,805)

8. Plaintiffs incorporate each of the preceding paragraphs 1 through 7 as if fully set forth herein.

9. Alcon Laboratories, Inc. holds the approved New Drug Application, No. 20-688, for Patanol® ophthalmic solution. The active ingredient of Patanol® is olopatadine hydrochloride. The New Drug Application was granted on December 18, 1996. Patanol® is approved for the treatment of the signs and symptoms of allergic conjunctivitis.

10. United States Patent No. 5,641,805 ("the '805 patent"), entitled "Topical Ophthalmic Formulations for Treating Allergic Eye Diseases" (Exhibit A hereto), was duly and

legally issued on June 24, 1997, to Alcon Laboratories, Inc. and Kyowa Hakko Kogyo Co. Ltd., as assignees of John Michael Yanni, Stella M. Robertson, Eiji Hayakawa, and Masashi Nakakura.

11. Alcon Laboratories, Inc. has assigned the '805 patent to Alcon Manufacturing, Ltd.

12. Alcon Laboratories, Inc. has been granted a license under the '805 patent and sells drug products covered by the '805 patent under the trademark Patanol® pursuant to a New Drug Application held by Alcon Laboratories, Inc. and approved by the FDA.

13. Plaintiffs will be substantially and irreparably damaged by infringement of the '805 patent.

14. By letter dated September 25, 2007 (the "Notice Letter"), Barr notified Alcon, Inc., Alcon Laboratories, Inc., Alcon Manufacturing, Ltd., and Kyowa that Barr had submitted an ANDA, No. 79-092, to the FDA. The purpose of the ANDA was to obtain approval under the Federal Food, Drug, and Cosmetic Act ("FDCA") to engage in the commercial manufacture, use, and sale of a drug product containing olopatadine hydrochloride prior to the expiration of the '805 patent.

15. Upon information and belief, the drug product containing olopatadine hydrochloride that is the subject of ANDA No. 79-092 is covered by one or more claims of the '805 patent.

16. In the Notice Letter, Barr also notified Alcon, Inc., Alcon Laboratories, Inc., Alcon Manufacturing, Ltd., and Kyowa that, as part of its ANDA, Barr had filed certifications pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

17. Barr's filing of the ANDA for the purpose of obtaining approval to engage in the commercial manufacture, use, or sale of a drug product containing olopatadine hydrochloride before the expiration of the '805 patent is an act of infringement of that patent under 35 U.S.C. § 271(e)(2)(A).

18. Upon information and belief, Barr acted without a reasonable basis for believing that it would not be liable for infringement of the '805 patent.

19. Unless Barr is enjoined from infringing the '805 patent, Plaintiffs will suffer irreparable injury. Plaintiffs have no adequate remedy at law.

COUNT II

(Patent Infringement – Patent No. 5,116,863)

20. Plaintiffs incorporate each of the preceding paragraphs 1 through 19 as if fully set forth herein.

21. Alcon Laboratories, Inc. holds the approved New Drug Application, No. 20-688, for Patanol® ophthalmic solution. The active ingredient of Patanol® is olopatadine hydrochloride. The New Drug Application was granted on December 18, 1996. Patanol® is approved for the treatment of the signs and symptoms of allergic conjunctivitis.

22. United States Patent No. 5,116,863 ("the '863 patent"), entitled "Dibenz[b,e]oxepin Derivative and Pharmaceutical Compositions Thereof" (Exhibit B hereto), was duly and legally issued on May 26, 1992, to Kyowa Hakko Kogyo Co. Ltd., as an assignee of Etsuo Oshima, Toshiaki Kumazawa, Shizuo Otaki, Hiroyuki Obase, Kenji Ohmori, Hidee Ishii, Haruhiko Manabe, Tadafumi Tamura, and Katsuichi Shuto.

23. Alcon Laboratories, Inc. has been granted a license under the '863 patent and sells drug products covered by the '863 patent under the trademark Patanol® pursuant to a

New Drug Application held by Alcon Laboratories, Inc. and approved by the FDA.

24. Plaintiffs will be substantially and irreparably damaged by infringement of the '863 patent.

25. By letter dated September 25, 2007 (the "Notice Letter"), Barr notified Alcon, Inc., Alcon Laboratories, Inc., Alcon Manufacturing, Ltd., and Kyowa that Barr had submitted an ANDA, No. 79-092, to the FDA. The purpose of the ANDA was to obtain approval under the FDCA to engage in the commercial manufacture, use, and sale of a drug product containing olopatadine hydrochloride prior to the expiration of the '863 patent.

26. Upon information and belief, the drug product containing olopatadine hydrochloride that is the subject of ANDA No. 79-092 is covered by one or more claims of the '863 patent.

27. In the Notice Letter, Barr also notified Alcon, Inc., Alcon Laboratories, Inc., Alcon Manufacturing, Ltd., and Kyowa that, as part of its ANDA, Barr had filed certifications pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

28. Barr's filing of the ANDA for the purpose of obtaining approval to engage in the commercial manufacture, use, or sale of a drug product containing olopatadine hydrochloride before the expiration of the '863 patent is an act of infringement of that patent under 35 U.S.C. § 271(e)(2)(A).

29. Upon information and belief, Barr acted without a reasonable basis for believing that it would not be liable for infringement of the '863 patent.

30. Unless Barr is enjoined from infringing the '863 patent, Plaintiffs will suffer irreparable injury. Plaintiffs have no adequate remedy at law.

WHEREFORE, Plaintiffs request the following relief:

(a) A judgment providing that the effective date of any FDA approval for Barr to commercially make, use, or sell olopatadine hydrochloride or any drug product containing olopatadine hydrochloride be not earlier than the later of the expiration dates of United States Patent Nos. 5,641,805 and 5,116,863;

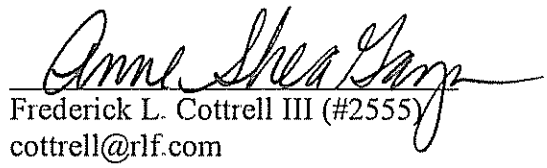
(b) A preliminary and permanent injunction against any infringement by Barr of United States Patent No. 5,641,805 through the commercial manufacture, use, sale, offer for sale, or importation into the United States of olopatadine hydrochloride or any drug product containing olopatadine hydrochloride;

(c) A preliminary and permanent injunction against any infringement by Barr of United States Patent No. 5,116,863 through the commercial manufacture, use, sale, offer for sale, or importation into the United States of olopatadine hydrochloride or any drug product containing olopatadine hydrochloride;

(d) A declaration that this is an exceptional case and an award of attorneys' fees pursuant to 35 U.S.C. § 285;

(e) Costs and expenses in this action; and

(f) Such further and other relief as this Court may deem just and proper.



Frederick L. Cottrell III (#2555)
cottrell@rlf.com
Anne Shea Gaza (#4093)
gaza@rlf.com
Richards, Layton & Finger P.A.
One Rodney Square
920 North King Street
Wilmington, DE 19801
(302) 651-7700
(302) 651-7701 (Facsimile)

Attorneys for Plaintiffs Alcon Manufacturing, Ltd., Alcon Laboratories, Inc., and Kyowa Hakko Kogyo Co., Ltd.

OF COUNSEL:

Bruce R. Genderson
Adam L. Perlman
Thomas H. L. Selby
Daniel P. Shanahan
Jessamyn S. Berniker
Eric K. Chiu
Williams & Connolly LLP
725 Twelfth Street, N.W.
Washington, DC 20005
(202) 434-5000
(202) 434-5029 (Facsimile)

Dated: November 7, 2007

EXHIBIT A

US005641805A

United States Patent [19]

Hayakawa et al.

[11] Patent Number: 5,641,805

[45] Date of Patent: Jun. 24, 1997

[54] **TOPICAL OPHTHALMIC FORMULATIONS FOR TREATING ALLERGIC EYE DISEASES**

[75] Inventors: **Eiji Hayakawa**, Susono; **Masashi Nakakura**, Shizuoka-ken, both of Japan; **Stella M. Robertson**, Arlington; **John Michael Yanni**, Burleson, both of Tex.

[73] Assignees: **Alcon Laboratories, Inc.**, Fort Worth, Tex.; **Kyowa Hakko Kogyo Co. Ltd.**, Tokyo, Japan

[21] Appl. No.: **469,729**

[22] Filed: **Jun. 6, 1995**

[51] **Int. Cl.**[6] **A61K 31/335**

[52] **U.S. Cl.** **514/450**

[58] **Field of Search** 514/450

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,871,865	10/1989	Lever, Jr. et al.	549/354
4,923,892	5/1990	Lever, Jr. et al.	514/450
5,116,863	5/1992	Oshima et al.	514/450

FOREIGN PATENT DOCUMENTS

0048023A2	3/1982	European Pat. Off. .
0214779A1	3/1987	European Pat. Off. .
0235796A2	9/1987	European Pat. Off. .

OTHER PUBLICATIONS

Kamei et al., "Effects of Certain Antiallergic Drugs on Experimental Conjunctivitis in Guinea Pigs," *Atarashi Ganka*, vol. 11(4), pp. 603–605 (1994) (abstract only).

Kamei et al., "Effect of (Z)–11–[3–(Dimethylamino) propylidene]–6,11–dihydrodibenz[b,e]oxepin–2–acetic Acid Hydrochloride on Experimental Allergic Conjunctivitis and Rhinitis in Rats and Guinea Pigs," Arzneimittelforschung, vol. 45(9), pp. 1005–1008 (1985).

Ohsima et al., "Synthesis and Antiallergic Activity of 11–(Aminoalkylidene)–6,11,dihydrodibenz[b,e]oxepin Derivatives," *J. Medicinal Chemistry*, vol. 35(11), pp. 2074–1084 (1992).

Sharif et al., "Characterization of the Ocular Antiallergic and Antihistaminic Effects of Olopatadine (AL–4943A), a Novel Drug for Treating Ocular Allergic Diseases," *J. of Pharmacology and Experimental Therapeutics*, vol. 278(3), pp. 1252–1261 (1996).

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Zhang et al., "Optically Active Analogues of Ebastine: Synthesis and Effect of Chirality on Their Antihistaminic and Antimuscarinic Activity," *Chirality*, vol. 6(8), pp. 631–641 (1994).

Church, "Is Inhibition of Mast Cell Mediator Release Relevant to the Clinical Activity of Anti–allergic Drugs?," *Agents and Actions*, vol. 18, 3/4, pp. 288–293 (1986).

Clegg et al., "Histamine Secretion from Human Skin Slices Induced by Anti–IgE and Artificial Secretagogues and the Effects of Sodium Cromoglycate and Salbutanol," *Clin Allergy*, vol. 15, pp. 321–328 (1985).

Hamilton et al., "Comparison of a New Antihistaminic and Antiallergic Compound KW 4679 with Terfenadine and Placebo on Skin and Nasal Provocation in Atopic Individuals," *Clinical and Experimental Allergy*, vol. 24, pp. 955–959 (1994).

Ikeda et al., "Effects of Oxatomide and KW–4679 on Acetylcholine–Induced Responses in the Isolated Acini of Guinea Pig Nasal Glands," *Int. Arch. Allergy Immunol.*, vol. 106, pp. 157–162 (1995).

Irani et al., "Mast Cell Heterogeneity," *Clinical and Experimental Allergy*, vol. 19, pp. 143–155 (1989).

Pearce et al., "Effect Disodium Cromoglycate on Antigen Evoked Histamine Release in Human Skin," *Clinical Exp. Immunol.*, vol. 17, pp. 437–440 (1974).

Siraganian, "An Automated Continuous Flow System for the Extraction and Fluorometric Analysis of Histamine," *Anal. Biochem.*, vol. 57, pp. 383–394 (1974).

"The Lung," *Scientific Foundations*, Raven Press, Ltd., New York, Ch. 3.4.11 (1991), Schwartz, pp. 601–615.

Kamei et al. "Effect of Certain Antirallergic Drugs on Experimental Conjunctivitis in Guinea Pigs", Atarashii Ganka 11(4) pp. 603–605 1994 (month unavailable).

Primary Examiner—Jeffrey C. Mullis

Attorney, Agent, or Firm—Patrick M. Ryan

[57] **ABSTRACT**

Topical ophthalmic formulations of the invention contain as an active ingredient 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid or a pharmaceutically acceptable salt thereof. The formulations are useful for treating allergic eye diseases such as allergic conjunctivitis, vernal conjunctivitis, vernal keratoconjunctivitis, and giant papillary conjunctivitis.

12 Claims, No Drawings

TOPICAL OPHTHALMIC FORMULATIONS FOR TREATING ALLERGIC EYE DISEASES

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to topical ophthalmic formulations used for treating allergic eye diseases, such as allergic conjunctivitis, vernal conjunctivitis, vernal keratoconjunctivitis, and giant papillary conjunctivitis. More particularly, the present invention relates to therapeutic and prophylactic topical use of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid for treating and/or preventing allergic eye diseases.

2. Description of the Related Art

As taught in U.S. Pat. Nos. 4,871,865 and 4,923,892, both assigned to Burroughs Wellcome Co. ("the Burroughs Wellcome Patents"), certain carboxylic acid derivatives of doxepin, including 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepine-2-carboxylic acid and 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepine-2(E)-acrylic acid, have antihistamine and antiasthmatic activity. These two patents classify the carboxylic acid derivatives of doxepin as mast cell stabilizers with antihistaminic action because they are believed to inhibit the release of autacoids (i.e., histamine, serotonin, and the like) from mast cells and to inhibit directly histamine's effects on target tissues. The Burroughs Wellcome Patents teach various pharmaceutical formulations containing the carboxylic acid derivatives of doxepin; Example 8 (I) in both of the patents discloses an ophthalmic solution formulation.

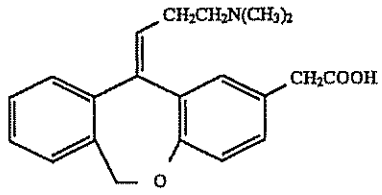
Although both of the Burroughs Wellcome Patents claim that the variety of pharmaceutical formulations disclosed are effective both for veterinary and for human medical use, neither patent contains an example demonstrating that the carboxylic acid derivatives of doxepin have activity in humans. Example 7 in the Burroughs Wellcome Patents demonstrates antihistamine activity in male guinea pigs and Example G demonstrates anaphylactoid activity in Wistar rats.

It is now well established, however, that the types of mast cells which exist in rodents are different from those in humans. See, for example, *THE LUNG: Scientific Foundations*, Raven Press, Ltd., New York, Ch. 3.4.11 (1991). Moreover, mast cell populations exist within the same species that differ in phenotype, biochemical properties, functional and pharmacological responses and ontogeny. These recognized differences in mast cells both between and within species are referred to as mast cell heterogeneity. See for example, Irani et al., "Mast Cell Heterogeneity," *Clinical and Experimental Allergy*, Vol. 19, pp. 143–155 (1989). Because different mast cells exhibit different responses to pharmacological agents, it is not obvious that compounds claimed to be anti-allergic ("mast cell stabilizers") will have clinical utility in specific mast cell populations. The assumption that mast cells are a homogeneous population and that therefore the effects of anti-allergic drugs observed in experiments in rat mast cells would be predictive of those in human cells is known to be incorrect. Church, "Is Inhibition of Mast Cell Mediator Release Relevant to the Clinical Activity of Anti-Allergic Drugs?," *Agents and Actions*, Vol. 18, 3/4, 288–293, at 291 (1986).

Examples exist in the art in which mast cell stabilizing drugs inhibit only select populations of mast cells. Disodium cromoglycate is an anti-allergic drug whose local effects are believed to be due to inhibition of mast cell degranulation (Church, *Agents and Actions*, at 288). This drug was shown to inhibit rodent mast cell degranulation. In human trials, 100 μM of the drug inhibited mast cells obtained from bronchoalveolar lavage fluid. In dispersed human lung mast cell preparations, 1000 μM of the drug was required to inhibit only 25% to 33% of histamine release. Finally, histamine release from human skin mast cells was not inhibited at all by disodium cromoglycate. Pearce et al., "Effect of Disodium Cromoglycate on Antigen Evoked Histamine Release in Human Skin," *Clinical Exp. Immunol.*, Vol. 17, 437–440 (1974); and Clegg et al., "Histamine Secretion from Human Skin Slices Induced by Anti-IgE and Artificial Secretagogues and the Effects of Sodium Cromoglycate and Salbutanol," *Clin. Allergy*, Vol. 15, 321–328 (1985). These data clearly indicate that classification of a drug as an anti-allergic does not predict that the drug possess inhibitory effects on all mast cell populations.

Topical ophthalmic formulations which contain drugs having conjunctival mast cell activity may only need to be applied once every 12–24 hours instead of once every 2–4 hours. One disadvantage to the ophthalmic use of reported anti-allergic drugs which in fact have no human conjunctival mast cell stabilizing activity is an increased dosage frequency. Because the effectiveness of ophthalmic formulations containing drugs which do not have conjunctival mast cell activity stems primarily from a placebo effect, more frequent doses are typically required than for drugs which do exhibit conjunctival mast cell activity.

U.S. Pat. No. 5,116,863, assigned to Kyowa Hakko Kogyo Co., Ltd., ("the Kyowa patent"), teaches that acetic acid derivatives of doxepin and, in particular, the cis form of the compound having the formula



(i.e., Z-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid), have anti-allergic and anti-inflammatory activity.

The Kyowa patent demonstrates anti-allergic activity and anti-inflammatory activity in Wistar male rats. Medicament forms taught by the Kyowa patent for the acetic acid derivatives of doxepin include a wide range of acceptable carriers; however, only oral and injection administration forms are mentioned. In the treatment of allergic eye disease, such as allergic conjunctivitis, such administration methods require large doses of medicine.

What is needed are topically administrable drug compounds which have demonstrated stabilizing activity on mast cells obtained from human conjunctiva, the target cells for treating allergic eye diseases. What is also needed are local administration methods for the treatment of allergic eye disease.

SUMMARY OF THE INVENTION

The present invention provides a method for treating an allergic eye disease characterized by administering to the eye a topical ophthalmic formulation which contains a therapeutically effective amount of 11-(3-

dimethylaminopropylidene) -6,11-dihydrodibenz[b,e] oxepin-2-acetic acid (referred to as "Compound A" hereinafter) or a pharmaceutically acceptable salt thereof. The formulation may contain the cis isomer of Compound A (Z-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz [b,e]oxepin-2-acetic acid), the trans isomer of Compound A (E-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz [b,e]oxepin-2-acetic acid), or a combination of both the cis and the trans isomers of Compound A, and unless specified otherwise,"11-(3-dimethylaminopropylidene)-6, 11-dihydrodibenz[b,e]oxepin-2-acetic acid" or "Compound A" means the cis isomer, the trans isomer or a mixture of both. "Cis isomer" means the cis isomer substantially free of the trans isomer; "trans isomer" means the trans isomer substantially free of the cis isomer. One isomer is "substantially free" of the other isomer if less than about two percent of the unwanted isomer is present.

Compound A has human conjunctival mast cell stabilizing activity, and may be applied as infrequently as once or twice a day in some cases. In addition to its mast cell stabilizing activity, Compound A also possesses significant antihistaminic activity. Thus, in addition to a prophylactic effect, Compound A will also have a therapeutic effect.

DETAILED DESCRIPTION OF THE INVENTION

Compound A is a known compound and both the cis and the trans isomers of Compound A can be obtained by the methods disclosed in U.S. Pat. No. 5,116,863, the entire contents of which are hereby incorporated by reference in the present specification.

Examples of the pharmaceutically acceptable salts of Compound A include inorganic acid salts such as hydrochloride, hydrobromide, sulfate and phosphate; organic acid salts such as acetate, maleate, fumarate, tartrate and citrate; alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as magnesium salt and calcium salt; metal salts such as aluminum salt and zinc salt; and organic amine addition salts such as triethylamine addition salt (also known as tromethamine), morpholine addition salt and piperidine addition salt.

The inhibitory effects of reported anti-allergic, mast cell stabilizing drugs on mast cells obtained from human conjunctiva (the target cells for topical ophthalmic drug preparations claimed useful in treating allergic conjunctivitis) were tested according to the following experimental method. Human conjunctival tissues obtained from organ/tissue donors were weighed and transferred to petri dishes containing RPMI 1640 culture medium supplemented with heat inactivated fetal bovine serum (20%, v/v), L-glutamine (2 mM), penicillin (100 units/ml), streptomycin (100 μg/ml), amphotericin B (2.5 μg/ml) and HEPES (10 mM) and equilibrated overnight at 37° C. (5% CO_2).

Post equilibration, tissues were placed in Tyrode's buffer (in mM: 137 NaCl, 2.7 KCl, 0.35 Na H_2PO_4, 1.8 $CaCl_2$, 0.98 $MgCl_2$, 11.9 Na HCO_3, 5.5 glucose) containing 0.1% gelatin (TGCM) and incubated with 200 U each of collagenase (Type IV) and hyaluronidase (Type I-S) per gram of tissue for 30 minutes at 37° C. Following enzyme digestion, tissues were washed with an equal volume of TGCM over Nitex® filter cloth (Tetko, Briarcliff Manor, N.Y.). Intact tissues were placed in TGCM for further enzymatic digestions.

The filtrate obtained from each digestion was centrifuged (825 g, 7 minutes) and pelleted cells were resuspended in calcium/magnesium free Tyrode's buffer (TG). Pooled cells from all digestions were centrifuged (825 g, 30 minutes) over a 1.058 g/L Percoll® cushion. Mast cell enriched cell pellets were resuspended and washed in TG buffer. Viability and number of mast cells were determined by vital dye exclusion and toluidine blue 0 staining of the harvested cell suspensions. Mast cell containing preparations were placed in supplemented RPMI 1640 culture medium and allowed to equilibrate at 37° C. prior to challenge with anti-human IgE (goat derived IgG antibody).

Cell suspensions containing 5000 mast cells were added to TGCM containing tubes and challenged with anti-human IgE. The final volume of each reaction tube was 1.0 mL. Tubes were incubated at 37° C. for 15 minutes post challenge. The release reaction was terminated by centrifugation (500 g, 7 minutes). Supernatants were collected and stored (−20° C.) until mediator analyses.

Initially, supernatants were analyzed for histamine content by both the automated fluorimetric method described by Siraganian, "An Automated Continuous Flow System for the Extraction and Fluorometric Analysis of Histamine," *Anal. Biochem.*, Vol. 57, 383–94 (1974), and a commercially available radioimmunoassay (RIA) system (AMAC, Inc., Westbrook, Me.). Results from these assays were positively correlated (r=0.999): therefore, the remainder of histamine analyses were performed by RIA.

Each experiment included an anti-human IgE (plus vehicle) positive release control, a spontaneous/vehicle release and a total histamine release control. Total histamine release was determined by treatment with Triton X-100® (0.1%). The experiments also included a non-specific goat IgG control. Test compounds are administered to the mast cell cultures either 1 or 15 minutes before stimulation with anti-human IgE. Inhibition of histamine release resulting from challenge of drug treated mast cells was determined by direct comparison with histamine release from vehicle treated, anti-IgE challenged mast cells using Dunnett's t-test (Dunnett, "A multiple comparison procedure for comparing treatments with a control, " *J. Amer. Stat Assoc.*, Vol. 50, 1096–1121 (1955)). The results are reported in Table 1. below.

As Table 1 clearly shows, the anti-allergic drugs disodium cromoglycate and nedocromil failed to significantly inhibit human conjunctival mast cell degranulation. In contrast, Compound A (cis isomer) produced concentration-dependent inhibition of mast cell degranulation.

TABLE 1

Compound Effect on Histamine Release from Human Conjunctival Tissue Mast Cells upon anti-Human IgE Challenge.

Compound	Dose (μM)	Treatment (min)	Inhibition (%)
Cromolyn sodium	1000	15	−15.4
	300	15	−6.9
	100	15	−1.2
	30	15	1.8
	10	15	10.6
Cromolyn sodium	1000	1	−9.4
	300	1	−1.8
	100	1	1.2
	30	1	0.1
	10	1	−0.9
Nedocromil sodium	1000	15	7.2
	300	15	11.3
	100	15	28.2*
	30	15	15.2
	10	15	9.2
	3	15	13.2
	1	15	10.7

TABLE 1-continued

Compound Effect on Histamine Release from Human Conjunctival Tissue Mast Cells upon anti-Human IgE Challenge.

Compound	Dose (μM)	Treatment (min)	Inhibition (%)
	0.3	15	3.7
	0.1	15	8.7
Nedocromil sodium	1000	1	−1.1
	300	1	4.0
	100	1	6.7
	30	1	−0.9
	10	1	−6.5
	3	1	0.8
	1	1	4.8
	0.3	1	8.8
	0.1	1	17.4
Compound A	2000	15	92.6*
	1000	15	66.7*
	600	15	47.5*
	300	15	29.6*
	100	15	13.0
	30	15	−3.9

*$p < 0.05$, Dunnett's t-test

Dunnett's t-test, is a statistical test which compares multiple treatment groups with one control group. In the assay described above, histamine released from drug treated mast cells are compared to histamine released from the anti-human IgE plus vehicle treated mast cells which serve as the positive control. Statistically significant inhibition is determined using this procedure. The probability level of 0.05 is accepted as the level of significance in biomedical research. Data indicated as significant have a low probability (0.05) of occurring by chance, indicating that the inhibition observed is an effect of the drug treatment.

The effects of the cis and trans isomers of Compound A on histamine release from human conjunctival tissue mast cells upon anti-human IgE challenge are compared in Table 2. The same experimental method used in Table 1 was used in Table 2. The results in Table 2 indicate that there is no statistically significant difference between the conjunctival mast cell activity of the two isomers at the indicated dose level.

TABLE 2

Isomeric Effect of Compound A on In-Vitro Histamine Release from Human Conjunctival Tissue Mast Cells upon anti-Human IgE Challenge.

Compound	Dose (μM)	Treatment (min)	Inhibition (%)
Compound A (cis)	500	15	29.7*∓
Compound A (trans)	500	15	26.2*∓

*$p < 0.05$, Dunnett's t-test compared to anti-IgE positive control.
∓not significantly different; $p > 0.05$ Studentized Range comparison of indicated doses

The topical activity of Compound A was tested in a passive anaphylaxis assay performed in rat conjunctiva. This assay indicates whether a topically applied compound effectively prevents or decreases the local allergic response in the conjunctiva. This assay allows an assessment of bioavailability following topical dosing. Briefly, male Sprague Dawley rats (6/group) were passively sensitized by subconjunctival injection of a rat serum containing IgE specific for ovalbumin (OA). Twenty-four hours post sensitization, test compound prepared in saline (0.9% NaCl) or saline vehicle was applied topically onto the sensitized eye. Twenty (20) minutes after dosing, rats were challenged intravenously via the lateral tail vein with 1.0 ml of a solution containing OA (1.0 mg/ml) and Evans Blue dye (2.5 mg/ml). Thirty (30) minutes post antigen challenge, animals were killed, skin was reflected, and the size of the resulting wheal and the intensity of the extravasated dye were determined. The wheal area multiplied by the dye intensity produced the individual response score. Scores for each group of animals were compared with the scores of the saline treated group using Dunnett's test and are listed in Table 3.

TABLE 3

In-Vivo Effects of Compound A on Passive Conjunctival Anaphylaxis in Rats

Compound	Conc. (%, w/v)	Permeability Score (× ± S.D.)	% Change
NaCl	0.9	239 ± 22	—
Compound B	0.1	133 ± 53*	−55
Compound C	0.1	139 ± 36*	−53
Compound A (cis)	0.1	55 ± 56*@	−86
Compound A (trans)	0.1	43 ± 34*@	−81

*$p < 0.01$, Dunnett's test
@$p < 0.05$, Studentized Range Comparison Procedure, significantly different from Compounds B and C.
Compound B = (Z)-11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenz [b,e]oxepin-2-carboxylic acid
Compound C = (Z)-11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenz [b,e]oxepin-2-acrylic acid

Compound A may be administered to the eye by means of conventional topical ophthalmic formulations, such as solutions, suspensions or gels. The preferred formulation for topical ophthalmic administration of Compound A is a solution. The solution is administered as eye drops. The preferred form of Compound A in the topical ophthalmic formulations of the present invention is the cis isomer. A general method of preparing the eye drops of the present invention is described below.

Compound A and an isotonic agent are added to sterilized purified water, and if required, a preservative, a buffering agent, a stabilizer, a viscous vehicle and the like are added to the solution and dissolved therein. The concentration of Compound A is 0.0001 to 5 w/v %, preferably 0.001 to 0.2 w/v %, and most preferably about 0.1 w/v %, based on the sterilized purified water. After dissolution, the pH is adjusted with a pH controller to be within a range which allows the use as an ophthalmologic medicine, preferably within the range of 4.5 to 8.

Sodium chloride, glycerin or the like may be used as the isotonic agent; p-hydroxybenzoic acid ester, benzalkonium chloride or the like as the preservative; sodium hydrogenphosphate, sodium dihydrogenphosphate, boric acid or the like as the buffering agent; sodium edetate or the like as the stabilizer; polyvinyl alcohol, polyvinyl pyrrolidone, polyacrylic acid or the like as the viscous vehicle; and sodium hydroxide, hydrochloric acid or the like as the pH controller.

If required, other ophthalmologic chemicals such as epinephrine, naphazoline hydrochloride, berberine chloride, sodium azulenesulfonate, lysozyme chloride, glycyrrhizate and the like may be added.

The eye drops produced by the above method typically need only be applied to the eyes a few times a day in an amount of one to several drops at a time, though in more severe cases the drops may be applied several times a day. A typical drop is about 30 μl.

Certain embodiments of the invention are illustrated in the following examples.

Example 1: Preferred Topical Ophthalmic Solution Formulation

Ingredient	Concentration (W/V %)
Compound A HCl	0.111*
Dibasic Sodium Phosphate (Anhydrous), USP	0.5
Sodium Chloride, USP	0.65
Benzalkonium Chloride	0.01
Sodium Hydroxide, NF	q.s. pH = 7.0
Hydrochloric Acid, NF	q.s. pH = 7.0
Purified Water	q.s. 100

*0.111% Compound A HCl is equivalent to 0.1% Compound A

Example 2: Topical Opthalmic Gel Formulation

Ingredient	Concentration (W/V %)
Compound A HCl	0.11*
Carbopol 974 P	0.8
Disodium EDTA	0.01
Polysorbate 80	0.05
Benzalkonium Chloride, Solution	0.01 + 5 xs
Sodium Hydroxide	q.s. pH 7.2
Hydrochloric acid	q.s. pH 7.2
Water for Injection	q.s. 100

*0.11% Compound A HCl is equivalent to 0.1% Compound A

What is claimed is:

1. A method for treating allergic eye diseases in humans comprising stabilizing conjuctival mast cells by topically administering to the eye a composition comprising a therapeutically effective amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz(b,e) oxepin-2-acetic acid or a pharmaceutically acceptable salt thereof.

2. The method of claim **1** wherein the composition is a solution and the amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e] oxepin-2-acetic acid is from about 0.0001 w/v. % to about 5% (w/v).

3. The method of claim **2** wherein the amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e] oxepin-2-acetic acid is from about 0.001 to about 0.2% (w/v).

4. The method of claim **3** wherein the amount of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e] oxepin-2-acetic acid is about 0.1% (w/v).

5. The method of claim **1** wherein the 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e] oxepin-2-acetic acid is (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e] oxepin-2-acetic acid, substantially free of (E)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e] oxepin-2-acetic acid.

6. The method of claim **5** wherein the amount of (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e] oxepin-2-acetic acid is from about 0.0001 to about 5% (w/v).

7. The method of claim **6** wherein the amount of (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e] oxepin-2-acetic acid is from about 0.001 to about 0.2% (w/v).

8. The method of claim **7** wherein the amount of (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e] oxepin-2-acetic acid is 0.1% (w/v).

9. The method of claim **1** wherein the 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e] oxepin-2-acetic acid is (E)-11-(3-dimethylaminopropylidene) -6,11 -dihydrodibenz[b,e] oxepin-2-acetic acid, substantially free of (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e] oxepin-2-acetic acid.

10. The method of claim **9** wherein the amount of (E)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz [b,e]oxepin-2-acetic acid is from about 0.0001 to about 5% (w/v).

11. The method of claim **10** wherein the amount of (E)-11-(3-dimethylaminopropylidene)-6,11-dihydredibenz [b,e]oxepin-2-acetic acid is from about 0.001 to about 0.2% (w/v).

12. The method of claim **11** wherein the amount of (E)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz [b,e]oxepin-2-acetic acid is about 0.1% (w/v).

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,641,805

DATED : June 24, 1997

INVENTOR(S) : Hayakawa et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the title page:

under "United States Patent [19]", "Hayakawa et al." should read "Yanni et al."

Item

[75] Inventors: **John Michael Yanni**, Burleson;
Stella M. Robertson, Arlington, both of Texas;
Eiji Hayakawa, Susono;
Masashi Nakakura, Shizuoka-ken, both of Japan

Signed and Sealed this

Eighteenth Day of August, 1998

Attest:

Attesting Officer

BRUCE LEHMAN

Commissioner of Patents and Trademarks

EXHIBIT B

US005116863A

United States Patent [19]

Oshima et al.

[11] Patent Number: 5,116,863

[45] Date of Patent: May 26, 1992

[54] **DIBENZ[B,E]OXEPIN DERIVATIVE AND PHARMACEUTICAL COMPOSITIONS THEREOF**

[75] Inventors: **Etsuo Oshima; Toshiaki Kumazawa; Shizuo Otaki; Hiroyuki Obase**, all of Shizuoka; **Kenji Ohmori**, Mishima; **Hidee Ishii**, Shizuoka; **Haruhiko Manabe**, Shizuoka; **Tadafumi Tamura**, Shizuoka; **Katsuichi Shuto**, Shizuoka, all of Japan

[73] Assignee: **Kyowa Hakko Kogyo Co., Ltd.**, Tokyo, Japan

[21] Appl. No.: **20,900**

[22] Filed: **Mar. 2, 1987**

[30] **Foreign Application Priority Data**

Mar. 3, 1986 [JP] Japan 61-45676

[51] **Int. Cl.**[5] **A61K 31/335**; C07D 313/12

[52] **U.S. Cl.** **514/450**; 548/215; 548/525; 549/354; 514/212; 514/228.2; 514/232.8; 514/253; 514/320; 514/374; 514/422; 540/596; 540/600; 544/62; 544/137; 544/147; 544/369; 544/375; 544/58.7; 546/196

[58] **Field of Search** 540/596, 602; 544/62, 544/137, 147, 369, 375, 98.7; 546/196; 548/215, 525; 549/354; 514/212, 222, 233, 234, 236, 237, 253, 320, 374, 422, 450, 228.2, 232.8

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Primary Examiner—Richard L. Raymond

Attorney, Agent, or Firm—Fitzpatrick, Cella, Harper & Scinto

[57] **ABSTRACT**

Novel dibenz[b,e]oxepin derivatives are employed in the treatment and control of allergic conditions such as allergic asthma and also employed in the treatment of inflammation.

3 Claims, No Drawings

DIBENZ[B,E]OXEPIN DERIVATIVE AND PHARMACEUTICAL COMPOSITIONS THEREOF

BACKGROUND OF THE INVENTION

Heretofore, it has been known that 11-unsubstituted, 11-hydroxy or 11-oxodibenz[b,e]oxepin derivative is used for antiinflammatory agents [J. Med. Chem., 21, 633–639 (1978)].

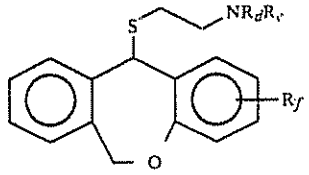
Further, it is known that dibenz[b,e]oxepin derivative wherein substitutents Ra and Rb at 11-position have the following definitions, is employed in the treatment and control of allergic conditions (U.S. Pat. No. 4,282,365)

Ra: H, OH, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, arylthio, NH_2, NHCHO or imidazolyl;

Rb: H or lower alkyl; or Ra and Rb taken together are =0, =CH—Rc wherein Rc is H or aryl.

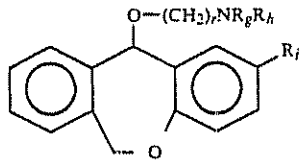
Furthermore, it is known that 11-(4-methylpiperazino) dibenz[b,e]oxepin derivative has an antiasthmatic activity (U.S. Pat. No. 4,396,550, U.S. Pat. No. 4,465.835, EP-A-38564).

It is also known that dibenz[b,e]oxepin derivative having the following formula:



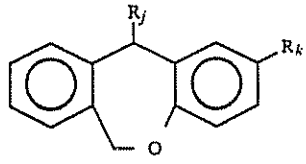
wherein Rd and Re are lower alkyl and Rf is lower alkyl or halogen, has an antiasthmatic activity (EP-A-85870).

Dibenz[b,e]oxepin derivative having an antiallergic activity and having the following structural formula:



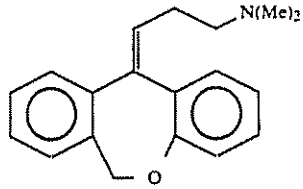
wherein Rg and Rh are alkyl, r is 2 or 3 and Ri is alkyl or halogen is known (JP-A-227879/84).

Dibenz[b,e]oxepin derivative having an antiallergic activity and having the following structural

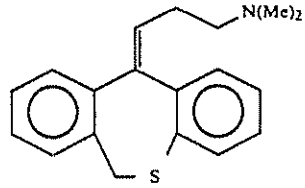


wherein Rj is 4-alkylpiperazino, 3-quinuclidylamino or —Xa—(CH_2)hd s—NR_lR_m wherein X_a is —NH—, —S— or —O—, s is 2 or 3 and R_l and R_m are alkyl, and R_k is CN, 5-tetrazolyl, $CONH_2$ or CO_2R_n wherein R_n is H, alkyl or 1-(ethoxycarbonyloxy)ethyl is known (EP-A-130555).

Doxepin having an antidepressant activity and having the following structural formula is known [Drugs, 13, 161 (1977)].



Dothiepin having an antidepressant activity and having the following structural formula is known [Arz.-Forsch., 13 1039 (1963); ibid., 14 100 (1964)].

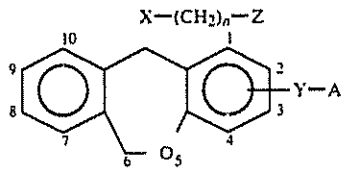


As the compound having both an antiallergic activity and an antiinflammatory activity, steroids are known.

It is always desired that a novel compound having an antiallergic activity or an antiinflammatory activity be developed

SUMMARY OF THE INVENTION

The present invention relates to a dibenz[b,e]oxepin derivative represented by the formula (I):



(I)

Wherein A represents a hydroxymethyl, a lower alkoxymethyl, a triphenylmethyloxymethyl, a lower alkanoyloxymethyl, a lower alkanoyl, a carboxy, a lower alkoxy carbonyl, a triphenylmethyloxycarbonyl, —$CONR_1R_2$ (wherein R_1 and R_2 are the same or different and represent hydrogen atom or lower alkyl) 4,4-dimethyl-2-oxazoline-2-yl group or —CONHOH; Y represents —$(CH_2)_m$—, —CHR_3—(CH_2)m— or —CR_4=CR_5—(CH_2)hd m— which is substituent at 2— or 3-position of the mother nucleus (wherein R_3 represents a lower alkyl, R_4 and R_5 are the same or different and represent a hydrogen atom or a lower alkyl, m is 0, 1, 2, 3 or 4, and the left side of the group of Y mentioned above is bound to benzen nucleus); X represents =N—, =CH— or —CH_2—; n is 0, 1, 2, 3 or 4; Z represents 4-methylpiperazino, 4-methylhomopiperazino, piperidino, pyrrolidino, thiomorpholino, morpholino, or —NR_6R_7 (wherein R_6 and R_7 are the same or different and represent a hydrogen atom or a lower alkyl); and ≡ means a single bond or double bond [hereinafter referred to as Compound (I) and Compounds with other formula numbers are hereinafter likewise referred to], and a pharmaceutically acceptable salt thereof. The present invention further pertains to a pharmaceutical

composition containing an effective amount of Compound (I) or a pharmaceutically acceptable salt thereof as an active ingredient, and a carrier or an excipient.

The present Compound (I) is useful for treatment of allergic conditions and inflammation.

DETAILED DESCRIPTION OF THE INVENTION

In the definition of each group of formula (I), the lower alkyl group includes straight or branched chain alkyl groups having 1 to 6 carbon atoms, for example, methyl, ethyl, n-propyl, iso-propyl, n-butyl, etc. In the definition of the group A, lower alkyl moiety of lower alkoxymethyl group and lower alkoxycarbonyl group has the same meaning as previously defined.

The lower alkoxymethyl group includes methoxymethyl, ethoxymethyl, n-propoxymethyl, isopropoxy, etc. and the lower alkoxycarbonyl group includes methoxycarbonyl, ethoxycarbonyl, etc.

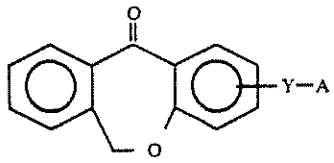
In the definition of the group A, the lower alkyl moiety of lower alkanoyl group and lower alkanoyloxymethyl group has the same meaning as previously defined.

The lower alkanoyl group includes formyl, acetyl, etc. and the lower alkanoyloxymethyl group includes formyloxymethyl, acetyloxymethyl, etc.

The pharmaceutically acceptable salt of Compound (I) includes pharmaceutically acceptable acid addition salt, metal salt, ammonium salt, organic amine addition salt, amino acid addition salt, etc.

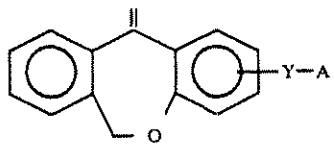
The pharmaceutically acceptable acid addition salt of Compound (I) includes inorganic acid salts such as hydrochloride, sulfate, phosphate, etc., and organic acid salts such as acetate, maleate, fumarate, tartrate, citrate, etc. The pharmaceutically acceptable metal salt includes alkalimetal salts such as sodium salt, potassium salt, etc., alkaline earch metal salts such as magnesium salt, calcium salt, etc., and alminium salt, zinc salt, etc. The pharmaceutically acceptable organic amine addition salt includes addition salt of morpholine and piperidine and the pharmaceutically acceptable amino acid addition salt includes addition salt of lysine, glysine, phenylalanine, etc.

Compound (I) is prepared by using a compound represented by the formula (II):



(II)

wherein Y and A have the same meanings as previously defined or a compound represented by the formula (III):



(III)

wherein Y and A have the same meanings as previously defined as the starting compound. Compound (II) is disclosed in J. Med. Chem., 19. 941 (1976), ibid., 20, 1499 (1977) and JP-A-21679/83.

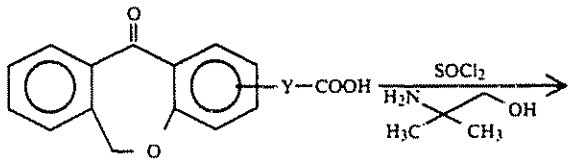
Compound (III) wherein —Y—A is —COOH is disclosed in JP-A-21679/83 and the other Compounds (III) can be prepared according to the method described in the publication though they do not occur in the publication.

The process for preparing Compound (I) is explained, depending on the kind of the group X.

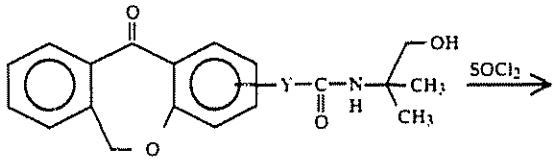
Process A

Synthesis of Compound (I) wherein X is =CH— (Part 1)

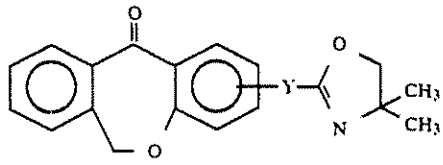
The carboxy group of Compound (IIa) is protected according to the following reaction scheme.



(IIa)



(IV)



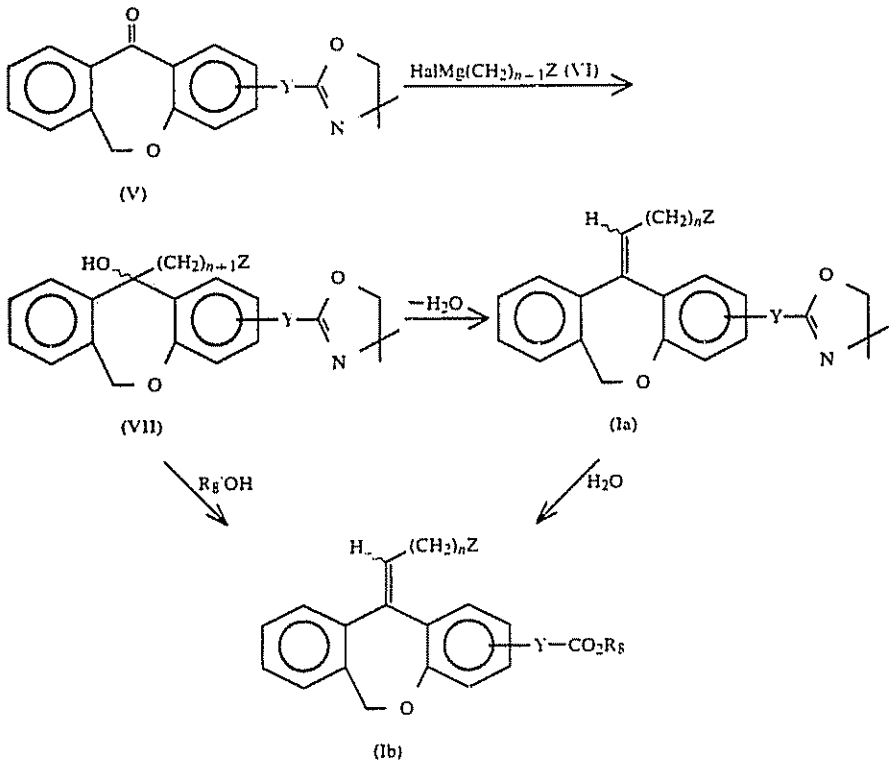
(V)

In the formulae, Y has the same meaning as previously defined, and Compound (IIa) is included in Compound (II) (compounds with an alphabet suffix following formula number are likewise included in compounds with common formula No.).

Compound (IIa) is reacted with 1 to 5 equivalents of thionyl chloride and 1 to 5 equivalents of 2-amino-2-methyl-1-propanol on the basis of Compound (IIa) in an inert solvent such as methylene chloride, if necessary in the presence of a base such as triethylamine at a temperature of from 0° C. to room temperature for 1–24 hours to form Compound (IV). Compound (IV) can also be obtained by reacting Compound (IIa) with thionyl chloride in advance and then with 2-amino-2-methyl-1-propanol.

Compound (IV) is reacted with 1–5 equivalents of thionyl chloride in an inert solvent such as methylene chloride, toluene and benzene at a temperature of from 0° C. to room temperature for 1–24 hours to form Compound (V).

Compounds (Ia) and (Ib) can be prepared from Compound (V) according to the following reaction scheme.



In the formulae. Y, Z, and n have the same meanings as previously defined, R_8 is hydrogen or a lower alkyl group, R'_8 is a lower alkyl group and Hal is halogen

As used herein, the term lower alkyl has the same meaning as that of lower alkyl in each group of formula (I). Halogen includes chlorine, bromine and iodine. Compound (V) is reacted with 1–5 equivalents of Compound (VI) in an inert solvent such as tetrahydrofuran and diethyl ether under atmosphere of an inert gas such as nitrogen and argon to form Compound (VII). The reaction is carried out at a temperature of from 0° C. to room temperature and is usually completed in 1–24 hours.

Compound (VII) is reacted with 1–5 equivalents of thionyl chloride or phosphoryl chloride in an inert solvent such as methylene chloride in the presence of a base such as pyridine to form Compound (Ia). The reaction is carried out at a temperature of from 0° C. to room temperature and is completed in 1–24 hours.

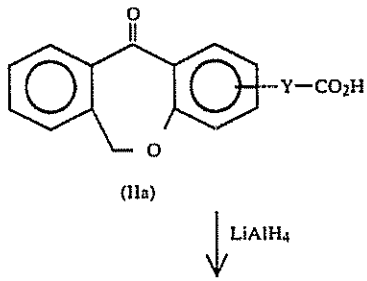
Compound (Ia) is incubated in an alcohol containing water, such as aqueous methanol solution, in the presence of an appropriate acidic catalyst such as p-toluenesulfonic acid at a temperature of from room temperature to the boiling point of the solvent to form Compound (Ib) wherein R_8 is H. The reaction is completed in 1–24 hours.

Compound (VII) is incubated in a alcohol of $R_8'OH$ in the presence of an appropriate acidic catalyst such as p-toluenesulfonic acid at a temperature of from room temperature to the boiling point of the solvent to form Compound (Ib) wherein R_8 is a lower alkyl. The reaction is completed in 1–24 hours.

Process B

Synthesis of Compound (I) wherein X is =CH— (Part 2)

The carboxy group of a compound represented by the formula (IIa) can be converted to a lower alkoxymethyl group or a trityloxymethyl group according to the following reaction scheme.



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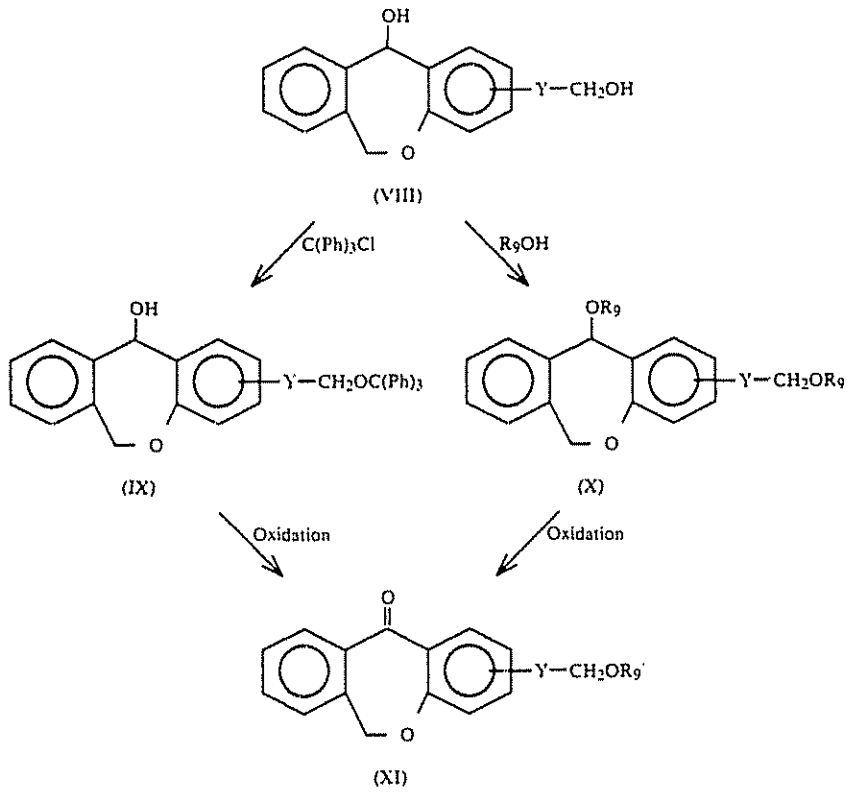


In the formulae, Y has the same meaning as previously defined, R_9 is a lower alkyl group and R_9' is a trityl group or a lower alkyl group. The term lower alkyl has the same meaning as that of lower alkyl in each group in formula (I).

Compound (IIa) is reduced with 1-5 equivalents of lithium aluminium hydride in tetrahydrofuran at a temperature of from 0° C. to room temperature for 1-24 hours to form Compound (VIII).

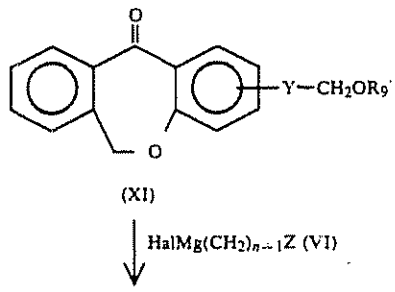
Compound (VIII) is reacted with 1-5 equivalents of trityl chloride in pyridine at a temperature of from room temperature to 100° C. for 1-24 hours to form Compound (IX).

Compound (IX) is oxidized with 1-5 equivalents of an appropriate oxidizing agent such as potassium permanganate and pyridinium chlorochromate in an inert solvent such as methylene chloride and acetone to form Compound (XI) wherein R_9' is trityl. The reaction is carried out at a temperature of from 0° C. to the boiling point of the solvent and is completed in 1-24 hours.

Compound (VIII) is incubated in an alcohol of R_9OH in the presence of an appropriate acidic catalyst such as sulfuric acid at a temperature of from room temperature to the boiling point of the solvent to form Compound (X). The reaction is usually completed in 1-24 hours.

Compound (X) is oxidized with 1-5 equivalents of an appropriate oxidizing agent such as Jones reagent in an inert solvent such as acetone to form Compound (XI) wherein R_9' is a lower alkyl. The reaction is carried out at a temperature of from 0° C. to the boiling point of the solvent and is usually completed in 1-24 hours.

The compounds represented by the formulae (Ic) and (Id) and if desired, the compound represented by the formula (Ie) can be synthesized from Compound (XI) according to the following reaction scheme.



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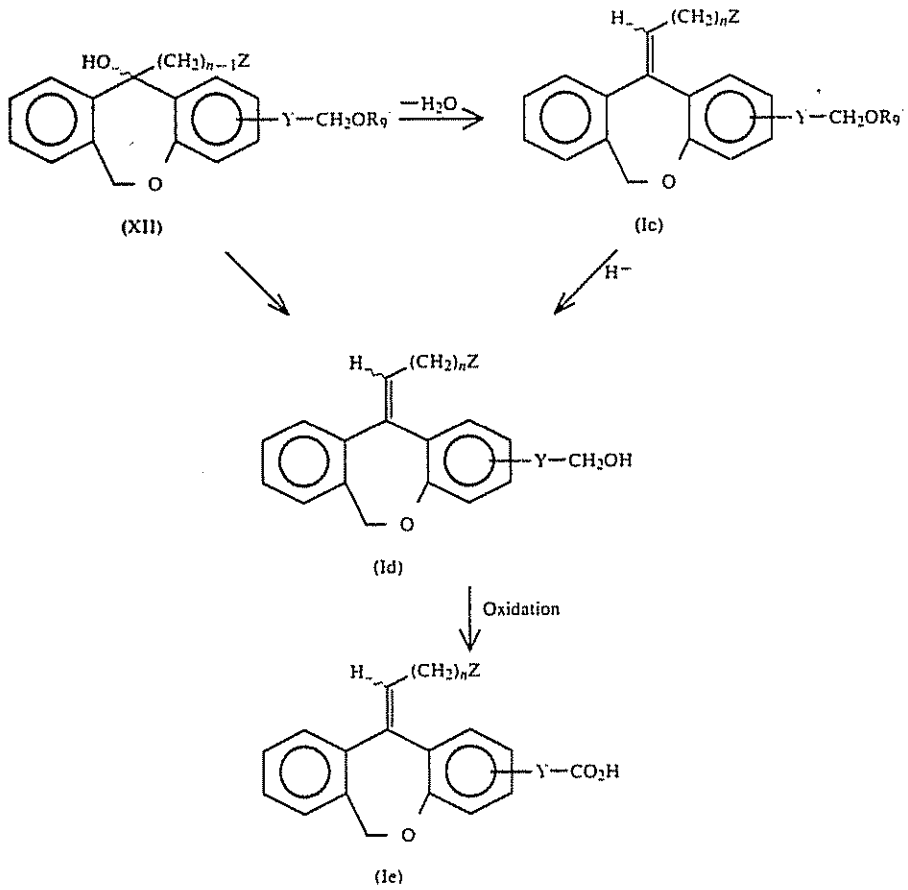


In the formulae, Y, Z, R_9', n and Hal have the same meanings as previously defined.

Compound (XI) is reacted with Compound (VI) which is Grignard reagent according to the same manner as in the reaction step from Compound (V) to Compound (VII) in Process A to form Compound (XII).

Compound (XII) is subjected to reaction according to the same manner as in the reaction step from Compound (VII) to Compound (Ia) in Process A to form Compound (Ic).

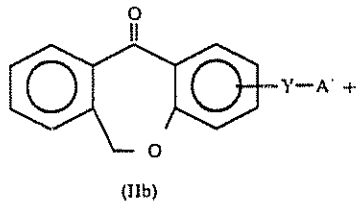
Compound (Ic) is incubated in a solvent containing water such as aqueous dioxane in the presence of an appropriate acidic catalyst such as p-toluenesulfonic acid at a temperature of from room temperature to the boiling point of the solvent to form Compound (Id). The reaction is usually completed in 1–24 hours.

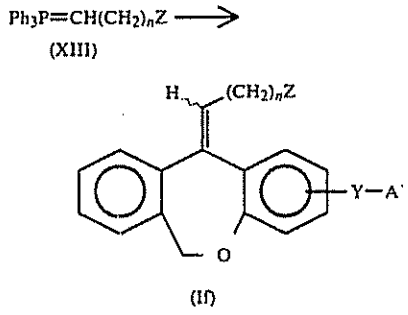
Compound (Id) can also be obtained in one step by incubating Compound (XII) in a solvent containing water such as aqueous dioxane in the presence of an appropriate acidic catalyst such as sulfonic acid at a temperature of from room temperature to the boiling point of the solvent. The reaction is usually completed in 1–24 hours.

If desired, Compound (Id) is oxidized with 1–5 equivalents of an appropriate oxidizing agent such as Jones reagent in an inert solvent such as acetone to form Compound (Ie). The reaction is carried out at a temperature of from 0° C. to the boiling point of the solvent and is usually completed in 1–24 hours.

Process C

Synthesis of Compound (I) wherein X is =CH— (Part 3)



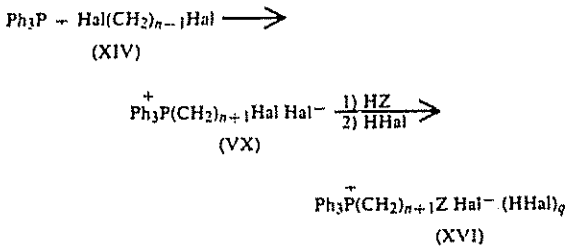


In the formulae, Y, Z, and n have the same meanings as previously defined. A' represents the groups falling within the definition of A but lower alkanoyl group.

Compound (IIb) is reacted with 1–5 equivalents of Compound (XIII) in an inert solvent such as tetrahy-

drofuran under atmosphere of an inert gas such as nitrogen and argon at a temperature of from 0° C. to room temperature for 1–24 hours to form Compound (Ij).

Compound (XIII) which is ylide, can be prepared according to the method described in C.A. 63 16366a (1965).



In the formulae, Hal, n and Z have the same meanings as previously defined and q is 1 or 2.

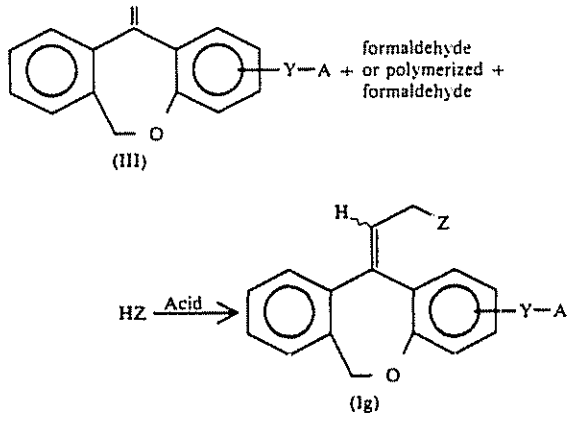
Compound (XIV) is reacted with an equivalent of triphenylphosphine in toluene at reflux of the solvent for 1–24 hours to form Compound (XV).

Compound (XV) is reacted with 1–5 equivalents of HZ in ethanol ar reflux of the solvent for 1–24 hours and excess HZ is distilled away under reduced pressure After the addition of 1–5 equivalents of HHal on the basis of Compound (XV), the mixture is incubated at a temperature of from 0° C. to the boiling point of the solvent for 1–24 hours to form Compound (XVI) which is Wittig reagent.

Compound (XVI) is treated with 1–2 equivalents of an appropriate base such as n-butyl lithium in an inert solvent such as tetrahydrofuran under atmosphere of an inert gas such as nitrogen and argon to form ylide (XIII). The reaction is carried out at −78° C. to room temperature and is usually completed in 1–24 hours.

Process D

Synthesis of Compound (I) wherein X is =CH— (Part 4)



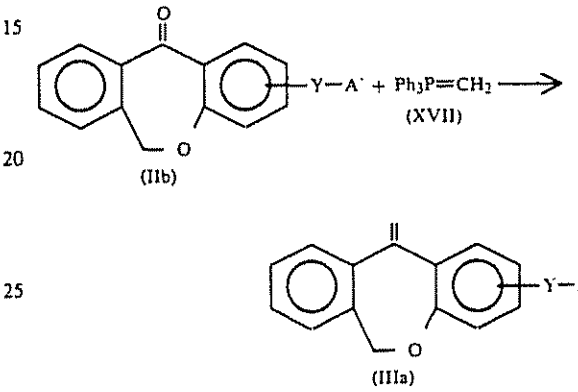
In the formulae, Y, Z and A have the same meanings as previously defined.

The process is known as Prince reaction [New Experimental Chemical Course (Maruzen), Vol. 14, Synthesis and Reaction of Organic Compound III, page 1375 (1977)].

Compound (III), 1 to 5 equivalents of formaldehyde and 1 to 5 equivalents of HZ are subjected to reaction in an inert solvent such as tetrachloroethane in the presence of an acid or reaction in an acid as such serving as a solvent under atmosphere of an inert gas such as nitrogen and argon to yield Compound (Ig)

The formaldehyde or polymerized formaldehyde includes p-formaldehyde, trioxane, etc. The acid includes acetic acid, trichloroacetic acid, trifluoroacetic acid, etc. The reaction is carried out at a temperature of from room temperature to the boiling point of the solvent and is completed in 1–24 hours.

Compound (III) which is the starting material can be prepared according to the process described in JP-A-21679/83, as shown below.



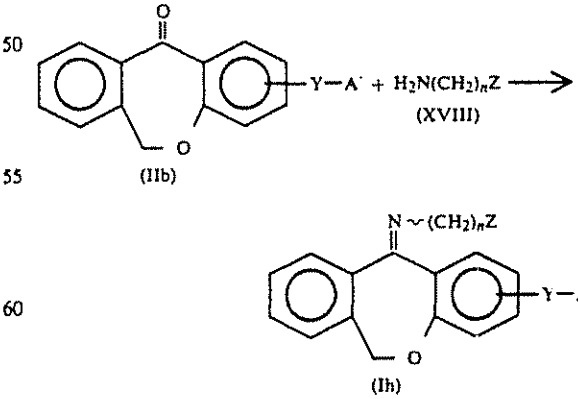
That is, Compound (IIb), 1 to 5 equivalents of methyltriphenylphosphonium bromide and 1 to 5 equivalents of n-butyl lithium on the basis of Compound (IIb) are subjected to reaction in an inert solvent at from −78° C. to room temperature for 1 to 5 hours to yield ylide (XVII) which is reacted with an equivalents of Compound (IIb) in an inert solvent at from −78° C. to room temperature under atmosphere of an inert gas for 1 to 24 hours to yield Compound (IIIa).

The inert gas includes nitrogen, argon, etc. and the inert solvent includes tetrahydrofuran. etc.

The group A′ in Compound (IIIa) can easily be converted to a lower alkanoyl group as is stated in Process I and therefore, Compound (III) can easily be prepared.

Process E

Synthesis of Compound (I) wherein X is=N—

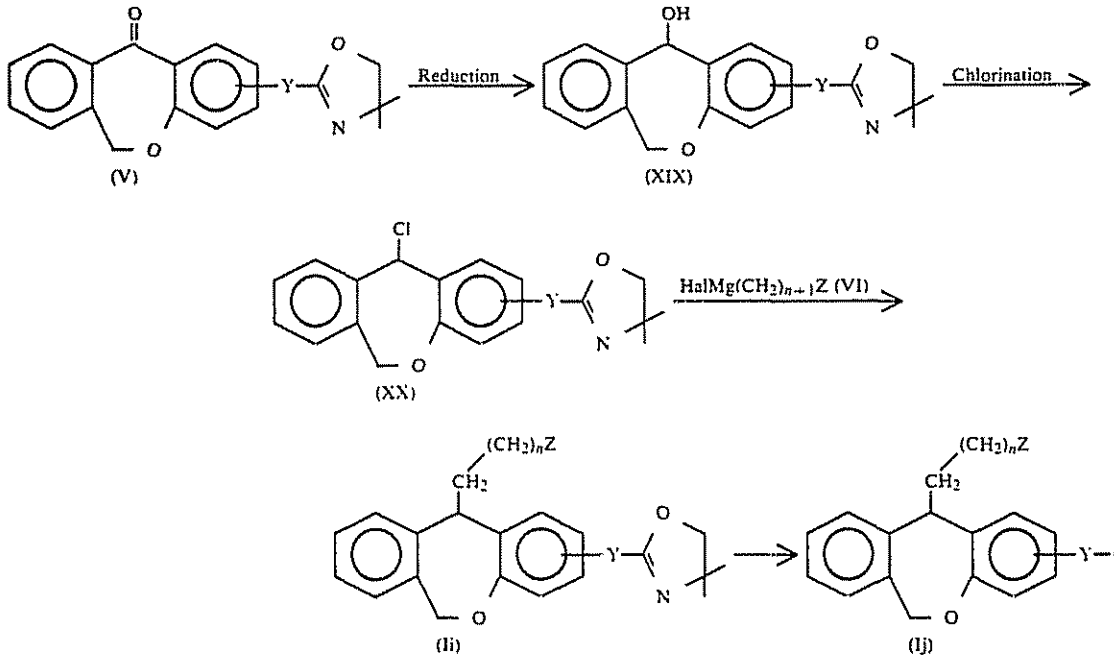


Compound (IIb) and 1 to 10 equivalents of Compound (XVIII) are subjected to reaction in an inert solvent such as benzene in the presence of 1 to 10 equivalents of titanium tetrachloride at from 0° C. to the

boiling point of the solvent under atmosphere of an inert gas such as nitrogen and argon for 1 to 48 hours to yield Compound (Ih).

Process F

Synthesis of Compound (I) wherein X is —CH_2— (Part 1)



In the formulae, Y, Z, n, R_8 and Hal have the same meanings as previously defined.

Compound (V) is reduced with 1 to 5 equivalent of lithium aluminium hydride or sodium borohydride in an inert solvent such as tetrahydrofuran and methanol at from 0° C. to room temperature for 1 to 24 hours to yield Compound (XIX).

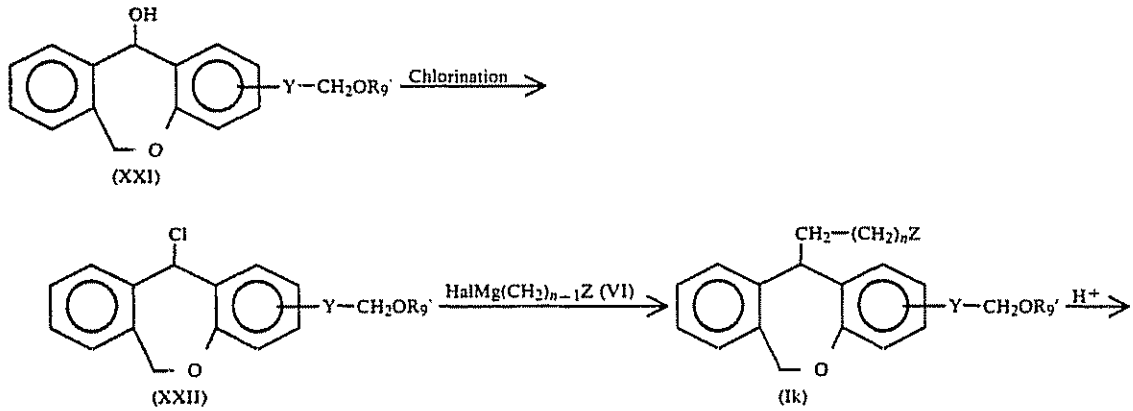
Compound (XIX) and 1 to 5 equivalents of thionyl chloride or phosphoryl chloride are subjected to reaction in an appropriate base such as pyridine at from 0° C. to room temperature to yield Compound (XX).

Compound (XX) and 1 to 5 equivalents of Compound (VI) are subjected to reaction in the same manner as in the reaction step from Compound (V) to Compound (VII) in Process A to yield Compound (Ii).

Compound (Ii) is subjected to reaction in the same manner as in the reaction step from Compound (VII) to Compound (Ib) or the reaction step from Compound (Ia) to Compound (Ib) in Process A to yield Compound (Ij)

Process G

Synthesis of Compound (I) wherein X is —CH_2— (Part 2)



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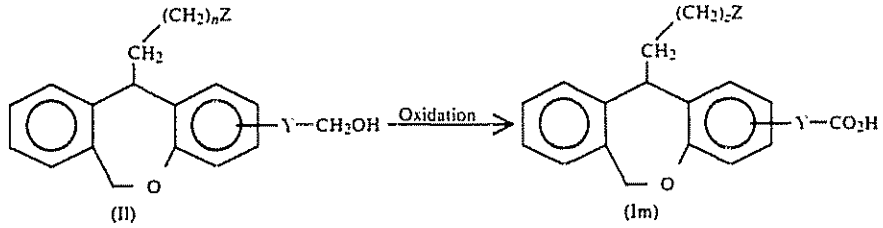


(II) (Im)

Compound (XXI) is subjected to chlorination in the same manner as in Process F to yield Compound (XXII). Compound (XXII) and Compound (VI) are subjected to reaction in the same manner as in Process F to yield Compound (Ik). Compound (Ik) is treated in the same manner as in Process B to form Compound (Il).

Compound (Il) is further treated to form Compound (Im).

Compound (IX) is included in the definition of the starting material (XXI).

Compound (XI) is reduced with 1 to 5 equivalents of lithium alminium hydride or sodium borohydride in an inert solvent such as tetrahydrofuran and methanol at from 0° C. to room temperature for 1 to 24 hours to yield Compound (XXI).

Process H

Synthesis of Compound (I) wherein X is —CH_2— (Part 3)

Compound (I) wherein X is —CH_2— can also be prepared by subjecting Compounds (Ia)–(Ig) obtained by the Processes A–D to reduction such as hydrogenation using paradium-carbon as catalyst.

The intermediates and the desired compounds in each of the processes described above can be purified and isolated by a purification method which is usually used in the field of organic chemical synthesis, such as filtration, extraction with organic solvent such as ethyl acetate and methylene chloride, drying, concentration, recrystallization, column chromatography, etc.

Out of Compounds (Ia)–(Ih) obtained in each of the processes described above, with regard to stereochemistry at 11-position of dibenz[b,e]oxepin, Compounds (Ia), (Ib), (Ic), (Id), (Ig) and (Ih) are apt to be formed as a trans-form and Compound (If) is apt to be formed as a cis-form, with high frequency compared with the other form.

When Compound (I) except Compounds (Ii)–(Im) is produced as a cis-trans mixture, Compound (I) is separated and purified by an appropriate method which is usually used in the field of organic chemical synthesis, such as column chromatography, recrystallization, etc.

If desired, cis-form can be converted to trans-form. For example, cis-form is added to an acetic acid and the mixture is heated at reflux in the presence of an appropriate catalyst such as p-toluenesulfonic acid for 1–24 hours to form trans-form.

With regard to the denotation of cis-form (or cin-form) and trans form (or anti-form) of Compound (I), Compound (I) wherein the substituent bound to the double bond is on the same side as oxygen of oxepin, is cis-form (or cin-form) and Compound (I) wherein the substituent is on the opposite side is trans-form (or anti-form).

Further, if cis- or trans-form is denoted according to E-Z expression, cis-form (or cin-form) is Z-form and trans-form (or anti-form) is E-form.

For example, the compound represented by the following formula is cis-form (or cin-form or Z-form).

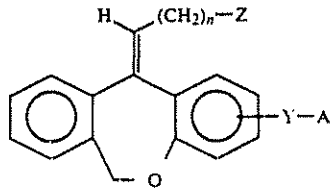


Table 1 shows examples of Compound (I) or pharmaceutically acceptable salts thereof and Table 2 shows the structural formula thereof.

Table 3 shows characteristic signals in NMR and Table 4 shows retention time in HPLC.

TABLE 1

Compound No.	Compound (I)
1	Methyl cis-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate Methyl trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate
2	Ethyl cis-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate Ethyl trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate
3	Cis-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid Trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid
4	Methyl cis-11-(3-diethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate Methyl trans-11-(3-diethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate
5	Cis-11-(3-diethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid Trans-11-(3-diethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid
6	Methyl cis-11-(3-pyrrolidinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate Methyl trans-11-(3-pyrrolidinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate
7	Cis-11-(3-pyrrolidinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid Trans-11-(3-pyrrolidinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid
8	Methyl cis-11-(4-dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate Methyl trans-11-(4-dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate
9	Cis-11-(4-dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid Trans-11-(4-dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid
10	Methyl cis-11-[2-(4-methylpiperazino)-ethylidene]-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate Methyl trans-11-[2-(4-methylpiperazino)-ethylidene]-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate

TABLE 1-continued

Compound No.	Compound (I)
11	Cis-11-[2-(4-methylpiperazino)ethylidene]-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid Trans-11-[2-(4-methylpiperazino)ethylidene]-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid
12	Methyl cis-11-(2-morpholinoethylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate Methyl trans-11-(2-morpholinoethylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate
13	Cis-11-(2-morpholinoethylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid Trans-11-(2-morpholinoethylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid
14	Methyl cis-11-(2-thiomorpholinoethylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate Methyl trans-11-(2-thiomorpholinoethylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate
15	Cis-11-(2-thiomorpholinoethylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid Trans-11-(2-thiomorpholinoethylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid
16	Methyl cis-11-(2-pyrrolidinoethylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate Methyl trans-11-(2-pyrrolidinoethylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate
17	Methyl cis-11-(2-piperidinoethylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate Methyl trans-11-(2-piperidinoethylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate
18	Methyl cis-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate Methyl trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate
19	Ethyl cis-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate Ethyl trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate
20	Cis-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid Trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid
21	Methyl cis-11-(4-dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate Methyl trans-11-(4-dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate
22	Cis-11-(4-dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid Trans-11-(4-dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid
23	Methyl cis-11-(3-pyrrolidinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate Methyl trans-11-(3-pyrrolidinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate
24	Cis-11-(3-pyrrolidinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid Trans-11-(3-pyrrolidinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid
25	Methyl cis-11-[2-(4-methylpiperazino)-ethylidene-6,11-dihydrodibenz[b,e]oxepin-2-acetate Methyl trans-11-[2-(4-methylpiperazino)-ethylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate
26	Cis-11-[2-(4-methylpiperazino)-ethylidene-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid Trans-11-[2-(4-methylpiperazino)-ethylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid
27	Methyl cis-3-[11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionate Methyl trans-3-[11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionate
28	Cis-3-[11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionic acid Trans-3-[11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionic acid
29	Methyl cis-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-3-acetate Methyl trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-3-acetate
30	Cis-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid Trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid
31	Cis-11-(3-dimethylaminopropylidene)-2-(2-hydroxyethyl)-6,11-dihydrodibenz[b,e]oxepin Trans-11-(3-dimethylaminopropylidene)-2-(2-hydroxyethyl)-6,11-dihydrodibenz[b,e]oxepin
32	Cis-11-(3-dimethylaminopropylidene)-2-(2-triphenylmethyloxymethyl)-6,11-dihydrodibenz-[b,e]oxepin Trans-11-(3-dimethylaminopropylidene)-2-(2-triphenylmethyloxymethyl)-6.11-dihydrodibenz-[b,e]oxepin
33	Cis-11-(3-dimethylaminopropylidene)-2-(3-hydroxypropyl)-6,11-dihydrodibenz[b,e]oxepin Trans-11-(3-dimethylaminopropylidene)-2-(3-hydroxypropyl)-6,11-dihydrodibenz[b,e]oxepin
34	Methyl cin-11-(2-diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate Methyl anti-11-(2-diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate
35	Cin-11-(2-diethylaminoethyl)imino-6.11-dihydrodibenz[b,e]oxepin-2-carboxylic acid Anti-11-(2-diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid
36	Methyl cin-11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate Methyl anti-11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate
37	Cin-11-(2-dimethylaminoethyl)imino-6.11-dihydrodibenz[b,e]oxepin-2-acetic acid Anti-11-(2-dimethylaminoethyl)imino-6.11-dihydrodibenz[b,e]oxepin-2-acetic acid
38	Methyl cin-11-(2-diethylaminoethyl)imino-6.11-dihydrodibenz[b,e]oxepin-2-acetate Methyl anti-11-(2-diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate
39	Cin-11-(2-diethylaminoethyl)imino-6.11-dihydrodibenz[b,e]oxepin-2-acetic acid Anti-11-(2-diethylaminoethyl)imino-6.11-dihydrodibenz[b,e]oxepin-2-acetic acid
40	Methyl cin-11-(3-dimethylaminopropyl)imino-6.11-dihydrodibenz[b,e]oxepin-2-acetate Methyl anti-11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate
41	Cin-11-(3-dimethylaminopropyl)imino-6.11-dihydrodibenz[b,e]oxepin-2-acetic acid Anti-11-(3-dimethylaminopropyl)imino-6.11-dihydrodibenz[b,e]oxepin-2-acetic acid
42	Methyl cin-3-[11-(2-diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionate Methyl anti-3-[11-(2-diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionate
43	Cin-[11-(2-diethylaminoethyl)imino-6.11-dihydrodibenz[b,e]oxepin-2-yl]-propionic acid Anti-[11-(2-diethylaminoethyl)imino-6.11-dihydrodibenz[b,e]oxepin-2-yl]-propionic acid
44	Methyl cin-2-[11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionate Methyl anti-2-[11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionate
45	Cin-2-[11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionic acid Anti-2-[11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionic acid
46	Methyl cin-11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetate Methyl anti-11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetate
47	Cin-11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid Anti-11-(2-dimethylaminoethyl)imino-6.11-dihydrodibenz[b,e]oxepin-3-acetic acid
48	Methyl cin-11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b.e]oxepin-3-acetate Methyl anti-11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetate
49	Cin-11-(3-dimethylaminopropyl)imino-6.11-dihydrodibenz[b,e]oxepin-3-acetic acid Anti-11-(3-dimethylaminopropyl)imino-6.11-

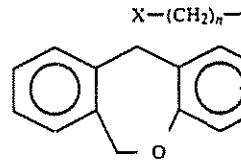
TABLE 1-continued

Compound No.	Compound (I)
	dihydrodibenz[b,e]oxepin-3-acetic acid
50	Methyl 11-(3-dimethylaminopropyl)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate
51	11-(3-dimethylaminopropyl)-6,11-dihydrodibenz-[b,e]oxepin-2-carboxylic acid
52	11-(3-dimethylaminopropyl)-6,11-dihydrodibenz-[b,e]oxepin-2-acetic acid
53	11-(3-Dimethylaminopropylidene)-2-(4,4-dimethyl-2-oxazoline-2-yl)-6,11-dihydrodibenz-[b,e]oxepin
54	11-(3-Dimethylaminopropyl)-2-(4,4-dimethyl-2-oxazoline-2-yl)-6,11-dihydrodibenz[b,e]oxepin
55	Methyl cis-11-(3-morpholinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate Methyl trans-11-(3-morpholinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate
56	Cis-11-(3-morpholinopropylidene)-6,11-dihydro-dibenz[b,e]oxepin-2-carboxylic acid Trans-11-(3-morpholinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid
57	Methyl cis-11-(3-thiomorpholinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate Methyl trans-11-(3-thiomorpholinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate
58	Cis-11-(3-thiomorpholinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid Trans-11-(3-thiomorpholinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid
59	Methyl trans-3-[cis-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-yl]-acrylate Methyl trans-3-[trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-yl]-acrylate
60	Trans-3-[cis-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-yl]-acrylic acid Trans-3-[trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-yl]-acrylic acid
61	Methyl cis-11-(3-methylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate Methyl trans-11-(3-methylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate
62	Cis-11-(3-methylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid Trans-11-(3-methylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid
63	Methyl cis-11-(3-aminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate Methyl trans-11-(3-aminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate
64	Cis-11-(3-aminopropylidene)-6,11-dihydrodibenz-[b,e]oxepin-2-acetic acid Methyl trans-11-(3-aminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid
3'	½ Fumarate · 1/5 hydrate of Compound 3 (trans form 99%)
5'	Fumarate · ½ hydrate of Compound 5 (cis form 99%)
7'	Fumarate · 1 hydrate of Compound 7 (cis form 70%)
11'	2 Fumarate · ½ hydrate of Compound 11 (trans form 100%)
13'	½ Fumarate · ½ hydrate of Compound 13 (trans form 93%)
15'	Fumarate of Compound 15 (trans form 100%)
20'	Fumarate · 3/2 hydrate of Compound 20 (trans form 95%)
26'	Fumarate · ½ hydrate of Compound 26 (trans form 88%)
28'	Fumarate · ½ hydrate of Compound 28 (trans form 63%)
31'	½ Fumarate · 1 hydrate of Compound 31 (trans form 95%)
33'	Fumarate of Compound 33 (cis form 100%)
35'	Sodium salt · 1 hydrate of Compound 35 (anti:cin = 1:1)

TABLE 1-continued

Compound No.	Compound (I)
43'	Sodium salt of Compound 43 (anti form 98%)
45'	Sodium salt 1 hydrate of Compound 45 (anti form 99%)
60'	Fumarate of Compound 60 (cis form 100%)

TABLE 2



Me: methyl group
Ph: pheny group
Et: ethyl group

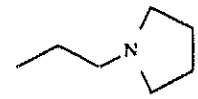
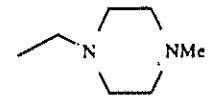
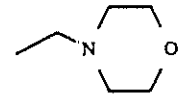
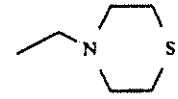
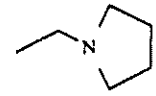
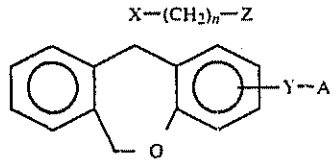
Compound No.	X	—Y—A	—(CH2)n—Z
1	CH	2-COOMe	
2	"	2-COOEt	"
3	"	2-COOH	"
4	"	2-COOMe	
5	"	2-COOH	"
6	"	2-COOMe	
7	"	2-COOH	"
8	"	2-COOMe	
9	"	2-COOH	"
10	"	2-COOMe	
11	"	2-COOH	"
12	"	2-COOMe	
13	"	2-COOH	"
14	"	2-COOMe	
15	"	2-COOH	"
16	"	2-COOMe	

TABLE 2-continued



Me: methyl group
Ph: pheny group
Et: ethyl group

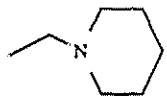
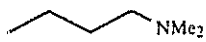
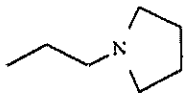
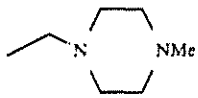
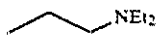
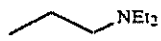
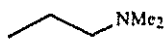
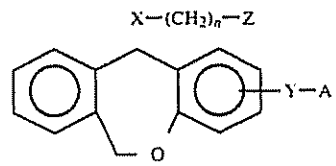
Compound No.	X	—Y—A	—(CH2)n—Z
17	"	2-COOMe	
18	CH	2-CH_2COOMe	
19	"	2-CH_2COOEt	"
20	"	2-CH_2COOH	"
21	"	2-CH_2COOMe	
22	"	2-CH_2COOH	"
23	"	2-CH_2COOMe	
24	"	2-CH_2COOH	"
25	"	2-CH_2COOMe	
26	"	2-CH_2COOH	"
27	"	2-CH_2CH_2COOMe	
28	"	2-CH_2CH_2COOH	"
29	"	3-CH_2COOMe	"
30	"	3-CH_2COOH	"
31	"	2-CH_2CH_2OH	"
32	"	2-CH_2CH_2OC(Ph)3	"
33	"	2-$CH_2CH_2CH_2$OH	"
34	N	2-COOMe	
35	"	2-COOH	"
36	"	2-CH_2COOMe	
37	"	2-CH_2COOH	"
38	N	2-CH_2COOMe	
39	"	2-CH_2COOH	"
40	"	2-CH_2COOMe	
41	"	2-CH_2COOH	"
42	"	2-CH_2CH_2COOMe	
43	"	2-CH_2CH_2COOH	"
44	"	2-$CH(CH_3)$COOMe	

TABLE 2-continued



Me: methyl group
Ph: pheny group
Et: ethyl group

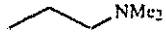
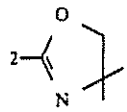
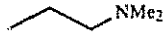
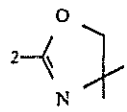
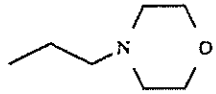
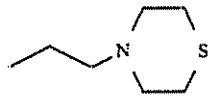
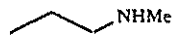
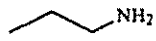
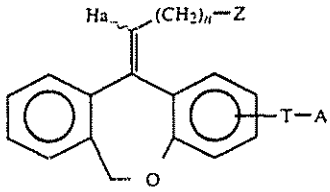
Compound No.	X	—Y—A	—(CH2)n—Z
45	"	2-$CH(CH_3)$COOH	"
46	"	3-CH_2COOMe	"
47	"	3-CH_2COOH	"
48	"	3-CH_2COOMe	
49	"	3-CH_2COOH	"
50	CH_2	2-COOMe	
51	"	2-COOH	"
52	"	2-CH_2COOH	"
53	CH		
54	CH_2		"
55	CH	2-COOMe	
56	"	2-COOH	"
57	CH	2-COOMe	
58	"	2-COOH	"
59	"	2-CH=CH—COOMe	
60	"	2-CH=CH—COOH	"
61	"	2-CH_2COOMe	
62	"	2-CH_2COOH	"
63	"	2-CH_2COOMe	
64	"	2-CH_2COOH	"

TABLE 3



Compound	Chemical sift of Ha proton (ppm) Cis	Trans	Measure solvent
1	5 67	6.06	A
2	5 70	6.07	A
3	5 72	6.09	B
4	5.69	6.05	A
5	5 73	—	B
6	5 70	6.07	A
7	5.71	6 09	B
8	5 70	6.08	A
9	5 71	6.08	B
10	5 85	6.22	A
11	—	6 11	B
12	5 81	6 20	A
13	5 81	6 13	B
14	5 81	6.18	A
15	5 80	6.13	B
16	5 83	6 19	A
17	5 92	6 28	A
18	5 69	6 06	A
19	5 70	6 07	B
20	5 66	6.00	B
21	5 66	6 02	B
22	5 67	6.02	B
23	5 69	5 99	A
24	5 60	5 92	A
25	5 84	6 17	A
26	5 72	6.05	B
27	5 69	6 57	A
28	5 50	5 99	B
31	5 66	5 99	A
32	5 69	6 97	A
33	5 65		A
55	5 67	6.06	A
56	5 73	6 10	B
57	5 68	6.03	A
58	5 70	6.08	B
59	5 72	—	A
60	5 71	—	B
61	5 63	—	A
62	5.65	—	B
63	5 68	—	A
64	5.67	—	B

A = $CDCl_3$
B = DMSO-d_6

TABLE 4

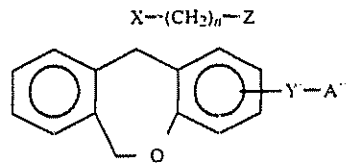
Compound	Retention time in HPLC (Minutes) Cis	Trans	Eluent
3	10.33	8 33	B
5	7.19	6 06	C
7	10.83	8.79	B
9	14.26	11 40	B
11	27 06	21 33	A
13	16 59	13 13	A
15	—	14.73	A
20	9 93	7.46	B
22	11 10	8 40	B
24	10.50	8.00	B
26	11 20	8 93	B
28	11 60	9 10	B
33	11 06	—	B
56	11 34	8 95	B
58	12 41	7.75	B
60	11 29	—	B
62	10.77	—	B

TABLE 4-continued

Compound	Retention time in HPLC (Minutes) Cis	Trans	Eluent
64	10.65	—	B

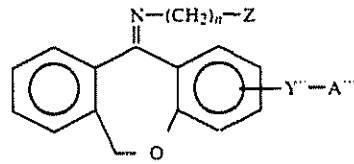
Instrument:	SHIMAZU LC-3A
Column	Yamamurakagaku YMC A-312
	A 0.01M PIC B-8
	in 54 3% MeOH
	B 0.01M PIC B-8
	in 61 3% MeOH
	C 0.01M PIC B-8
	in 66.0% MeOH
• PIC:	PIC reagent (Produced by Water Associates)
Pressure:	85–95 kg/cm^2
Temperature:	room temperature

Compound (I) has both an antiallergic activity and antiinflammatory activity. Among Compound (I), the compound represented by the formula (I') has strong antiallergic activity and the compound represented by the formula (II') has strong antiinflammatory activity



(I')

In the formula, X, n and Z are as previously defined, —Y'—A'' is —Y—A when X is =CH— or —CH_2— and is —Y—A which is bound at 2 position of the mother nucleus when X is =N—, and Y and A are as previously defined.



(II')

In the formula, n and Z are as previously defined; Y''' is —CH_2— or —CHR_3— substituted at 2 or 3 position of the mother nucleus wherein R_3 is a lower alkyl; A''' is a hydroxymethyl, a loweralkoxymethyl, a triphenylmethyloxymethyl, a lower alkanoyloxymethyl, a formyl, a carboxyl, a lower alkoxycarbonyl, a triphenylmethyloxycarbonyl, —$CONR_1R_2$ wherein R_1 and R_2 are the same or different and are hydrogen atom or a lower alkyl, 4,4-dimethyl-2-oxazoline-2-yl or —CONHOH.

The antiallergic activity and antiinflammatory activity of Compound (I) are described below:

Test for antiallergic activity

Antiallergic activity was investigated by a homologous PCA (passive cutaneous anaphlaxis) of rats for 48 hours, where Wistar male rats having body weights of 180 to 220 g were used for sampling of antiserum and Wistar male rats having body weights of 120 to 140 g were used for the PCA test.

A) Preparation of anti EWA rat serum

Anti-egg white albumin (EWA) rat serum was prepared according to Stotland and Share's method [Canad. J. Physiol. Pharmacol. 52, 1114 (1974)]. That is, 1 mg of EWA was mixed with 20 mg of aluminum hydroxide gel and 0.5 ml of mixed vaccine of pertussis, diphtheria and tetanus, and the mixture was subcutaneously administered in four portions into rat's footpad. After 14 days, blood was sampled from the carotid artery, and the serum was separated from the sampled blood, and preserved under freezing at −80° C. The potency of the antiserumin in the homologous PCA for 48 hours was 1:32.

B) Homologous PCA test of rats for 48 hours

Groups each consisting of 3 rats were used, and 0.05 ml of anti-EWA rat serum diluted with a physiological saline solution to 8 times as much was incutaneously injected each at two positions of depilated back to make the animals passively sensitised. After 47 hours, the compound of the present invention, or its solution (physiological saline solution or CMC solution) was orally administered. One hour thereafter, 0.5 ml/100 g of 1% Evan's blue physiological saline solution containing 2 mg of the antigen EWA was administered into the tail vein, and 30 minutes thereafter, the animals were sacrificed by exsanguination. Then, the skins were stripped and the amount of leaked pigment at the blue-dyed parts was measured according to the Katayama et al method [Microbiol. Immunol. 22, 89 (1978)]. That is, the blue-dyed parts were cut out by scissors, and placed in test tubes containing 1 ml of 1N KOH and incubated at 37° C. for 24 hours. Then, 9 ml of a mixture of 0.6N phosphoric acid and acetone (5:13) was added thereto, and the mixture was shaked and centrifuged at 2,500 rpm for 10 minutes. Absorbancy of the supernatant at 620 μm was measured, and the amount of leaked pigment was quantitatively determined by the calibration curve prepared in advance. An average of measurements at the two position was made a value for one zooid, and inhibition rate for the individual zooid was calculated by the following formula:

$$\text{Inhibition rate (\%)} = \frac{\text{Average leaked amount of solvent-administered group} - \text{Leaked amount of test compound-administered group}}{\text{Average leaked amount of solvent-administered group}} \times 100$$

Cases where, the inhibition rate is 50% or higher, were regarded as positive PCA inhibition activity, and the minimum administered dosage, where a positive case was observed in at least one of three zooids was regarded as minimum effective dosage (MED). The results are shown in Table 5.

Acute Toxic Test

Groups each consisting of 3 dd, male mice having body weights of 20±1 g were used, and the compound of the present invention was administered orally (po: 300 mg/kg) or intraperitoneally (ip: 100 mg/kg). Mortality 7 days after the administration was observed to obtain MLD (minimum lethal dosage). The results are shown in Table 5.

Antiinflammatory Activity Test

Antiinflammatory activity was examined according to Rat carageenin paw edema [J. Pathol. 104, 15-29 (1971)]. Groups each consisting of three Wistar male rats weighing 150 g were used. The test compound was suspended in 0.3% aqueous CMC solution and the suspension was given orally. Sixty minutes later, 0.1 ml of 0.1% carageenin was subcutaneously injected in a hind paw to form carageenin paw edema.

The volume of paw was measured before the administration and 3 hours after the administration of carageenin with plethysmometer.

The ratio of the volume 3 hours after the administration to that before the administration of carageenin was calculated and each ratio is compared with the ratio of control group (0.3% CMC was administered) to give the edema inhibiting percentage. The results are shown in Table 6.

TABLE 5

Compound	Acute toxicity (MLD) mg/kg po	Acute toxicity (MLD) mg/kg ip	Antiallergic Activity Number of positive zooids in one group of 3 zooids Dosage mg/kg 100	10	1	0.1	0.01	0.001	M E D mg/kg
3 (cis)	>300	>100	3/3	3/3	3/3	3/3	0/3	—	0.1
3' (trans)	>300	>100	3/3	2/3	1/3	1/3	0/3	—	0.1
5' (cis)	>300	>100	3/3	3/3	3/3	0/3	0/3	—	1
7' (cis:trans = 7:3)	>300	>100	3/3	2/3	1/3	0/3	—	—	1
9 (cis:trans = 91:9)	>300	>100	3/3	3/3	2/3	0/3	0/3	—	1
11' (trans)	>300	>100	2/3	1/3	0/3	0/3	—	—	10
13' (cis:trans = 7:93)	>300	>100	3/3	1/3	0/3	0/3	—	—	10
15' (trans)	—	—	3/3	0/3	0/3	0/3	—	—	100
20' (trans)	>300	>100	3/3	3/3	3/3	1/3	0/3	—	0.1
20	>300	>100	2/3	2/3	3/3	3/3	0/3	0/3	0.1

TABLE 5-continued

Compound	Acute toxicity (MLD) mg/kg po	Acute toxicity (MLD) mg/kg ip	Antiallergic Activity Number of positive zooids in one group of 3 zooids Dosage mg/kg 100	10	1	0.1	0.01	0.001	M E D mg/kg
(trans) 20	>300	>100	3/3	3/3	3/3	3/3	1/3	0/3	0.01
(cis) 22	>300	>100	3/3	3/3	2/3	1/3	0/3	—	0.1
(cis:trans = 92:8) 26'	>300	>100	3/3	3/3	2/3	0/3	—	—	1
(cis:trans = 12:88) 28'	>300	>100	3/3	3/3	3/3	2/3	2/3	0/3	0.01
(cis:trans = 37:63) 28	>300	>100	3/3	2/3	3/3	1/3	0/3	—	0.1
(cis) 28	>300	>100	3/3	3/3	2/3	2/3	1/3	0/3	0.01
(trans) 31'	>300	>100	3/3	3/3	3/3	1/3	0/3	—	0.1
(trans) 31	>300	>100	3/3	3/3	2/3	3/3	0/3	—	0.1
(trans) 31	300	>100	—	3/3	3/3	2/3	0/3	0/3	0.1
(cis) 33'	NT	NT	3/3	3/3	1/3	0/3	—	—	1
(cis) 35'	300>	100>	3/3	1/3	0/3	—	—	—	10
(cin:anti = 1:1) 37	300>	100>	3/3	3/3	0/3	—	—	—	10
(cin:anti = 8:92) 39	300>	100>	3/3	2/3	3/3	0/3	—	—	1
(cin:anti = 2:98) 41	300>	100>	3/3	2/3	1/3	0/3	—	—	1
(cin:anti = 3:97) 43'	300>	100>	3/3	2/3	0/3	0/3	—	—	10
cin:anti mixture 45'	300>	100>	3/3	3/3	2/3	0/3	—	—	1
(anti) 56'	>300	>100	3/3	3/3	3/3	1/3	0/3	—	0.1
(cis:trans = 87:13) 58	>300	>100	3/3	3/3	3/3	0/3	—	—	1
(cis:trans = 87:13) 60'	>300	>100	3/3	3/3	2/3	1/3	0/3	—	0.1
(cis)									

TABLE 6

Compound No.	Carageenin paw edema inhibiting percentage (%) (Average value in one group of 3 rats. 100 mg/kg oral administration)
37	51.6
39	50.2
41	38.7
45'	63.1
47	46.0
49	24.1

As is evidenced in Tables 5 and 6, Compound (I) and pharmaceutically acceptable salt thereof have PCA inhibiting activity and/or carageenin paw edema inhibiting activity.

PCA inhibiting activity is believed to be on the basis of an activity inhibiting liberation of chemical mediator such as histamine from fat skin cell. Therefore, Compound (I) and pharmaceutically acceptable salts thereof are believed to be useful for treating an allergic disease such as bronchus asthma which is caused by trachea contractile activity of chemical mediator such as histamine.

On the other hand, carageenin paw edema inhibiting activity is believed to be on the basis of prostaglandin biosynthesis inhibiting activity. Thus, Compound (I) and pharmaceutically acceptable salts thereof are believed to be useful for treating an acute inflammation and rheumatism which are ascribed to excessive prostaglandin.

Compound (I) includes a compound having both antiallergic and antiinflammatory activities described above which is useful for the treatment of allergic diseases accompanied by inflammation.

In view of the pharmacological activity of Compound (I), Compound (I) can be used in various medicament forms for the administration purposes.

The present medicament composition can be prepared by uniformly mixing an effective amount of a free Compound (I) or a pharmaceutically acceptable salt thereof as an active component with a pharmaceutically

acceptable carrier or excipient. The carrier can take a wide range of forms in accordance with a desirable medicament form for the administration. These medicament compositions are desirably in a unit dosage form suitable for the oral administration or injection administration. In the preparation of a composition in the oral dosage form, any useful, pharmaceutically acceptable carrier can be used. For example, an oral liquid preparation such as a suspended medicament or syrup medicament can be prepared using water; sugars such as sucrose, sorbitol, fructose, etc.; glycols such as polyethylene glycol, propylene glycol, etc.; oils such as sesame oil, olive oil, soybean oil, etc.; antiseptics such as alkyl parahydroxybenzoate, etc.; and flavors such as strawberry flavor, peppermint, etc. Powder, pills, capsules and tablets can be prepared using an excipient such as lactose, glucose, sucrose, mannitol, etc.; a disintegrator such as starch, sodium alginate, etc.; a lubricant such as magnesium stearate, talc, etc.; a binder such as polyvinyl alcohol, hydroxypropylcellulose, gelatin, etc.; a surfactant such as fatty acid esters; and a plasticizer such as glycerine, etc. Tablets and capsules are the most useful, oral unit dosage forms because of easy administration. To prepare tablets and capsules, solid carriers for medicament are used. Injection solution can be prepared using a carrier consisting of a salt solution, a glucose solution or a mixture of the salt solution and the glucose solution. The effective dosage of Compound (I) is 1 to 20 mg/kg/day for a human being, and number of administration is 3 to 4 per day.

Examples and Reference Examples are given below:

REFERENCE EXAMPLE 1

(Raw material 1) Methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate

In this example, 348.9 g of sodium salt of methyl p-hydroxybenzoate, 402.4 g of phthalide and 200 g of sodium chloride are mixed with one another and stirred at 150° C. for 6 hours. After completion of the reaction, the mixture is cooled until the temperature is brought back to room temperature, 4 l of aqueous 10% acetic acid solution is added thereto and the mixture is allowed to stand at room temperature overnight. After stirring the mixture at room temperature for 3 hours, deposited crystals are separated by filtration, and 6 l of water is added thereto. After stirring the mixture at room temperature for 30 minutes, the deposited crystals are separated by filtration. After the addition of 3 l of toluene to the crystals, the mixture is stirred at room temperature for one hour. The crystals are separated by filtration and dried over heating under reduced pressure to yield 393.9 g of 2-(4-methoxycarbonylphenoxy) methyl benzoic acid.

IR (KBr disk): 3400, 1700, 1610, 1260, 1235 cm^{-1} The thus obtained 2-(4-methoxycarbonylphenoxy) methyl benzoic acid (392.7 g) is suspended in 5.0 l of methylene chloride and 266.0 g of trifluoroacetic anhydride is added thereto. After stirring the mixture at room temperature for one hour, 19.4 g of boron trifluoride-ethylether complex is added thereto and the mixture is stirred at room temperature for two hours. The reaction solution is poured into ice water. After an organic solvent layer is separated from the mixture, the organic layer is washed with diluted aqueous sodium hidroxide solution and water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain 335.3 g of methyl 11-oxodibenz[b,e]oxepin-2-carboxylate as a white crystal.

Melting point and elementary analysis are shown in Table 7.

IR (KBr disk): 1710, 1650, 1610, 1250, 1010 cm^{-1}

NMR ($CDCl_3$, δ, ppm): 3.84(s, 3H), 5.14(s, 2H), 6.87–8.93(m, 7H)

REFERENCE EXAMPLES 2–5

(Raw material 2) 11-Oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid

(Raw material 3) 11-Oxo-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid

(Raw material 4) 2-(11-Oxo-6,11-dihydrodibenz[b,e]oxepin-2-yl)-propionic acid

(Raw material 5) 3-(11-Oxo-6,11-dihydrodibenz[b,e]oxepin-2-yl)-propionic acid

Raw materials 2–5 are produced by respectively substituting p-hydroxyphenyl acetic acid, m-hydroxyphenyl acetic acid, 2-(p-hydroxyphenyl)-propionic acid and 3-(p-hydroxyphenyl)-propionic acid for methyl p-hydroxybenzoate in Reference example 1.

Melting points and elementary analyses thereof are shown in Table 7.

REFERENCE EXAMPLE 6

(Raw material 6) Methyl 11-methylene-6,11-dihydrodibenz-[b,e]oxepin-2-carboxylate

In 100 ml of tetrahydrofuran is suspended 25 g of methyltriphenylphosphonium bromide and 40 ml of 1.6 N-n-butyl lithium helium hexane solution is dropwise added thereto under a nitrogen atmosphere and ice-cooling. After stirring the mixture under ice-cooling for 30 minutes, a solution obtained by dissolving 15 g of methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate in 250 ml of tetrahydrofuran is dropwise added thereto and the mixture is stirred at room temperature for two hours. The solvent is distilled away under reduced pressure and the residue is purified by column chromatography on silica gel (eluent: hexane:ethyl acetate=3:1) to obtain 3.7 g of the desired product as a colorless oily matter.

NMR ($CDCl_3$, δ, ppm): 3.83(s, 3H), 5.15(s, 2H), 5.29 (s, 1H), 5.74(s, 1H), 6.69–8.22(m, 7H)

Melting point and elementary analysis are shown in Table 7.

REFERENCE EXAMPLE 7

(Raw material 7) Methyl 11-methylene-6,11-dihydrodibenz-[b,e]oxepin-2-acetate

The desired product is obtained by substituting 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid for methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate in Reference example 6.

Colorless oily matter

NMR ($CDCl_3$, δ, ppm): 3.48(s, 2H), 3.61(s, 3H), 5.05 (s, 2H), 5.20(s, 1H), 5.62(s, 1H), 6.59–7.43 (m, 7H)

IR (neat, cm^{-1}): 2950, 1740, 1615, 1490, 1010

Melting point and elementary analysis are shown in Table 7.

REFERENCE EXAMPLE 8

(Raw material 8) 11-Methylene-6,11-dihydrodibenz[b,e]-oxepin-2-acetic acid

To a mixed solvent of 200 ml of methanol and 50 ml of 2N-aqueous sodium hydroxide solution is added 2.9 g

of methyl 11-methylene-6,11-dihydrodibenz[b,e]oxepin-2-acetate (raw material 7, Reference example 7) and the mixture is heated at reflux for two hours. After allowing the mixture to stand for cooling, the mixture is concentrated under reduced pressure, and the pH of the mixture is adjusted to 1.0 with aqueous 4N-hydrochloric acid solution. The mixture is extracted with 500 ml of ethyl acetate, washed with aqueous 1N-hydrochloric acid solution and saturated aqueous sodium chloride solution in order and dried over anhydrous sodium sulfate. The solvent is distilled away under reduced pressure and the resultant crude product is crystallized from hexane to obtain 2.7 g of the desired product as a white solid.

NMR (DMSO-d_6+D_2O, δ, ppm): 3.45(s, 2H), 5.02(s, 2H), 5.16(s, 1H), 5.60(s, 1H), 6.45–7.44(m, 7H)

Melting point and elementary analysis are shown in Table 7.

REFERENCE EXAMPLE 9

(Raw material 9) Methyl 11-methylene-6,11-dihydrodibenz-[b,e]oxepin-3-acetate

The desired product is obtained by substituting 11-oxo-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid for methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate in Reference example 6.

REFERENCE EXAMPLE 10

(Raw material 10) 11-Methylene-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid

The desired product is obtained by substituting methyl 11-methylene-6,11-dihydrodibenz[b,e]oxepin-3-acetate for methyl 11-methylene-6,11-dihydrodibenz[-b,e]oxepin-2-acetate in Reference example 8.

TABLE 7

Raw material	Melting point (°C.)	Elementary analysis (%) or mass spectrum		
1	128–129	as $C_{16}H_{12}O_4$		
			C	H
	(Isopropyl	Calculated	71.63	4.51
	ether)	Found	71.55	4.48
2	130–132	as $C_{16}H_{12}O_4$		
			C	H
	(Ethyl	Calculated	71.63	4.51
	acetate)	Found	71.86	4.55
3	111–114	as $C_{16}H_{12}O_4$		
			C	H
	(Ethyl	Calculated	71.63	4.51
	acetate)	Found	71.53	4.66
4	Syrup	as $C_{17}H_{14}O_4$ (M + 282)		
5	144–145	as $C_{17}H_{14}O_4$		
			C	H
	(Water)	Calculated	72.33	5.00
		Found	72.45	5.20
6	Syrup	as $C_{17}H_{14}O_3$ (M + 266)		
7	Syrup	as $C_{18}H_{16}O_3$ (M + 280)		
8	162–163	as $C_{17}H_{14}O_3$		
			C	H
	(Water)	Calculated	76.68	5.30
		Found	76.29	5.16

REFERENCE EXAMPLE 11

(Reagent 1) (3-Dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide

In this example, 350.0 g of triphenylphosphine and 270.0 g of dibromopropane are suspended in 700 ml of toluene and the suspension is heated at reflux for 25 hours. After allowing the suspension to stand for cooling, the formed product is separated by filtration and washed with 2 l of toluene to obtain 550.0 g of (3-bromopropyl)-triphenylphosphonium bromide hydrobromide having m.p. 233–234° C.

Then, 100.0 g of (3-bromopropyl)-triphenylphosphonium bromide hydrobromide is suspended in 500 ml of ethanol and 300 ml of 50% aqueous dimethylamine solution is added thereto. After heating the mixture at reflux for 10 minutes, the mixture is allowed to stand for cooling. The solvent is distilled away under reduced pressure and the resultant crude product is recrystallized from ethanol to obtain 64.0 g of the desired product having the physicochemical properties as identified in Table 8.

REFERENCE EXAMPLES 12–14

(Reagent 2) (3-Diethylaminopropyl)-triphenylphosphonium bromide hydrobromide ½ hydrate

(Reagent 3) (4-Dimethylaminobutyl)-triphenylphosphonium bromide hydrobromide

(Reagent 4) (3-Pyrrolidinopropyl)-triphenylphosphonium bromide hydrobromide ½ hydrate

The above-captioned compounds are prepared according to the same manner as in Reference example 11 and the physicochemical properties are shown in Table 8.

TABLE 8

Reagent	Melting point (°C.)	Elementary analysis (%)			
1	287–289 (Ethanol)	as $C_{23}H_{28}NPBr_2$			
			C	H	N
		Calculated	54.24	5.54	2.75
		Found	54.12	5.63	2.93
2	228–230 (Isopropanol)	as $C_{25}H_{32}NPBr_2{\cdot}\frac{1}{2}H_2O$			
			C	H	N
		Calculated	55.33	6.05	2.58
		Found	55.31	6.19	2.68
3	255–257 (Isopropanol)	as $C_{24}H_{30}NPBr_2$			
			C	H	N
		Calculated	55.09	5.78	2.68
		Found	55.04	5.91	2.62
4	291–293 (Ethanol)	as $C_{25}H_{30}NPBr_2{\cdot}\frac{1}{2}H_2O$			
			C	H	N
		Calculated	55.17	5.74	2.57
		Found	55.18	5.95	2.66

EXAMPLE 1

Ethyl 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[-b,e]oxepin-2-carboxylate (Compound 2)

Process A:

N-(1,1-dimethyl-2-hydroxyethyl)-11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-carboxamide

In this process, 12.5 g of 6,11-dihydro-11-oxodibenz[-b,e]oxepin-2-carboxylic acid is dissolved in 300 ml of methylene chloride and 8.9 g of thionyl chloride is dropwise added to the solution under ice-cooling. After stirring the mixture at room temperature for two hours,

the solvent is distilled away under reduced pressure. To the obtained residue are added 100 ml of toluene and 32.4 g of 2-amino-2-methyl-propanol, and the mixture is stirred at 50° C. for 3 hours.

The mixture is extracted with 500 ml of ethyl acetate, and washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order. The mixture is dried over anhydrous sodium sulfate and the solvent is distilled away under reduced pressure. The crude product is recrystallized from toluene to obtain 8.3 g of the desired product as a white crystal.

Melting point: 155–159° C.

NMR ($CDCl_3$ +DMSO-d_6, δ, ppm): 1.38(s, 6H), 3.53(s, 2H), 5.25(s, 2H), 6.91–8.68(m, 7H)

Process B:
2-(4,4-Dimethyl-2-oxazoline-2-yl)-11-oxo-6,11-dihydrodibenz[b,e]oxepin

In this process, 8.0 g of N-(1,1-dimethyl-2-hydroxyethyl)-11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-carboxamide is suspended in 100 ml of methylene chloride. To the suspension is added 3.6 g of thionyl chloride under a nitrogen atmosphere and ice-cooling and the mixture is stirred at room temperature for one hour. To the mixture is added 300 ml of methylene chloride, and the mixture is washed with saturated aqueous sodium bicarbonate solution and dried over anhydrous magnesium sulfate. The solvent is distilled away under reduced pressure and the residue is purified by column chromatography on silica gel (eluent: hexane:ethyl acetate=2:1). The resultant crude product is recrystallized from hexane to obtain 6.3 g of the desired product as a white crystal.

Melting point: 122° C.

NMR ($CDCl_3$, δ, ppm): 1.37(s, 6H), 4.06(s, 2H), 5.14(s, 2H), 6.84–8.89(m, 7H)

Elementary analysis (%): as $C_{19}H_{17}O_3N$:
Calculated: C 74.25, H 5.58, N 4.56,
Found: C 74.23, H 5.55, N 4.59.

Process C:
11-(3-Dimethylaminopropyl)-11-hydroxy-2-(4,4-dimethyl-2-oxazoline-2-yl)-6,11-dihydrodibenz[b,e]oxepin

To a solution of 3-dimethylaminopropyl magnesium chloride obtained by reacting 1.2 g of magnesium with 6.0 g of 3-dimethylaminopropyl chloride in 80 ml of tetrahydrofuran under a nitrogen atmosphere using dibromoethane as a catalyst is dropwise added under ice-cooling 80 ml of tetrahydrofuran solution of 7.6 g of 2-(4,4-dimethyl-2-oxazoline-2-yl)-11-oxo-6,11-dihydrodibenz[b,e]oxepin.

After stirring the mixture at room temperature overnight, aqueous ammonium chloride solution is added thereto and then the mixture is neutralized with aqueous 4N-hydrochloric acid solution. The solvent is distilled away under reduced pressure. To the residue is added aqueous 4N-hydrochloric acid solution to adjust the pH of the solution to 1. After washing the mixture with 200 ml of diethyl ether, aqueous 10N-sodium hydroxide solution is added to adjust the pH of the mixture to 13. The mixture is extracted with 200 ml of methylene chloride and the extract is washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order. After drying the solution over anhydrous sodium sulfate, the solvent is distilled away under reduced pressure. The residue is purified by column chromatography on silica gel (eluent: hexane:ethyl acetate triethylamine=10:10:1). The resultant crude product is triturated with isopropyl ether to obtain 6.1 g of the desired product as a white solid.

Melting point: 166–167° C.

NMR ($CDCl_3$, δ, ppm): 1.30(s, 8H), 2.18(s, 8H), 3.98 (s, 2H), 4.97 and 5.46(ABq, J=15.1 Hz, 2H), 6.65–8.49(m, 7H)

Process D: Ethyl
11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate

In this process, 6.1 g of 11-(3-dimethylaminopropyl)-11-hydroxy-2-(4,4-dimethyl-2-oxazoline-2-yl)-6,11-dihydrodibenz[b,e]oxepin is dissolved in 300 ml of ethanol. To the solution are added 0.6 g of p-toluenesulfonic acid and 30 ml of water and the mixture is heated at reflux for 4 hours. The solvent is distilled away under reduced pressure to obtain a crude product of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid. The crude product is dissolved in 300 ml of ethanol and 20 ml of concentrated sulfuric acid is added thereto. The mixture is heated at reflux for 15 hours.

The solvent is distilled away under reduced pressure. To the resultant residue is added 200 ml of water and the mixture is washed with diethyl ether. The pH of the mixture is adjusted to 12.0 with aqueous 10N-sodium hydroxide solution and the mixture is extracted with 300 ml of methylene chloride. The extract is washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order. After drying the extract over anhydrous sodium sulfate, the solvent is distilled away under reduced pressure and the resultant residue is purified by column chromatography on silica gel (eluent: ethyl acetate:triethylamine=10:1) to obtain 1.4 g of the desired product as a colorless oily matter.

IR (neat, cm^{-1}): 2950, 2775, 1715, 1250, 1120, 1010
Mass spectrum (m/z): 351 (M^+)

EXAMPLE 2

11-(3-Dimethylaminopropylidene)-2-(2-triphenylmethyloxymethyl)-6,11-dihydrodibenz[b,e]oxepin (Compound 32)

Process A:
11-Hydroxy-2-(2-hydroxyethyl)-6,11-dihydrodibenz[b,e]oxepin

In this process, 20 g of methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetate is dissolved in 500 ml of tetrahydrofuran. To the solution is added 6.0 g of lithium alminium hydroxide and the mixture is stirred at room temperature for one hour. After decomposing an excess of the reagent by the addition of water to the solution, the mixture is filtered to remove an inorganic salts and the filtrate is concentrated to dryness under reduced pressure to obtain 17.7 g of the desired product as a white solid.

Melting point: 132–136° C.

NMR ($CDCl_3$+DMSO-d_6+D_2O, δ, ppm): 2.59(t, 2H, J=6.8Hz), 3.55(t,2H, J=6.8Hz), 4.89 and 5.71(ABq, 2H, J=12.6Hz), 5.60(s, 1H), 6.46–7.49(m, 7H)

Process B:

11-Hydroxy-2-(2-triphenylmethyloxyethyl)-6,11-dihydrodibenz[b,e]oxepin

In this process, 17.2 g of 11-hydroxy-2-(2-hydroxyethyl)-6,11-dihydrodibenz[b,e]oxepin is dissolved in 50 ml of pyridine. To the solution is added 30 g of triphenylchloromethane and the mixture is stirred at 50° C. for 5 hours. After adding water and stirring the mixture for 2 hours, the solvent is distilled away under reduced pressure. The mixture is extracted with 1000 ml of ethyl acetate, washed with saturated aqueous sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent is distilled away under reduced pressure and the resultant residue is purified by column chromatography on silica gel (eluent: hexane:ethyl acetate=3:1) to obtain 21.7 g of the desired product as a colorless amorphous.

NMR ($CDCl_3+D_2O$, δ, ppm): 2.47–2.95(m, 2H), 2.96–3.45(m, 2H), 4.87 and 5.71(ABq, 2H, J=13.2Hz), 5.43(s, 1H), 6.33–7.51(m, 22H)

Process C:

11-Oxo-2-(2-triphenylmethyloxyethyl)-6,11-dihydrodibenz[b,e]oxepin

In this process, 10 g of 11-hydroxy-2-(2-triphenylmethyloxyethyl)-6,11-dihydrodibenz[b,e]oxepin is dissolved in a solution comprising 800 ml of acetone, 1000 ml of water, 20 ml of saturated aqueous magnesium sulfate solution and 0.2 g of disodium phosphate. To the solution is dropwise added 2.6 g of aqueous sodium permanganate solution and the mixture is stirred at room temperature for 4.5 hours. Then, 100 ml of methanol is added thereto and the mixture is heated at reflux for 3 hours. After allowing the mixture to stand for cooling, the mixture is filtered and the filtrate is extracted with 1000 ml of ethyl acetate, washed with saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. The solvent is distilled away under reduced pressure and the resultant crude product is recrystallized from isopropanol to obtain 8.0 g of the desired product having melting point of 132–134° C. as a white crystal.

Elementary analysis (%): as $C_{35}H_{28}O_3$

Calculated: C 84.65, H 5.68,

Found: C 84.56, H 5.67.

NMR ($CDCl_3$, δ, ppm): 2.61–3.04(m, 2H), 3.05–3.46 (m, 2H), 5.01(s, 2H), 6.63–8.07(m, 22H)

Process D:

11-(3-Dimethylaminopropyl)-11-hydroxy-2-(2-triphenylmethyloxyethyl)-6,11-dihydrodibenz[b,e]oxepin

To a solution of 3-dimethylaminopropyl magnesium chloride obtained by reacting 0.2 g of magnesium with 1.0 g of 3-dimethylaminopropyl chloride in 10 ml of tetrahydrofuran under a nitrogen atmosphere using dibromoethane as a catalyst, is dropwise added a solution obtained by dissolving 2.0 g of 11-oxo-2-(2-triphenylmethyloxyethyl)-6,11-dihydrodibenz[b,e]oxepin in 10 ml of tetrahydrofuran under ice cooling and the mixture is stirred at room temperature for one day. Aqueous ammonium chloride solution is added thereto and the pH of the mixture is adjusted to 7.0 with aqueous 4N-hydrochloric acid solution. The solvent is distilled away under reduced pressure. The mixture is extracted with 200 ml of methylene chloride and washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order. After drying the extract over anhydrous sodium sulfate, the solvent is distilled away under reduced pressure. The resultant residue is purified by column chromatography on silica gel (eluent: hexane:ethyl acetate:triethylamine=10:10:1) to obtain 1.2 g of the desired product as a colorless amorphous

NMR ($CDCl_3$, δ, ppm): 0.85–1.83(m, 4H), 2.08(s, 6H), 2.67–3.44(m, 6H), 4.94 and 5.36(ABq, 2H, J=15.8Hz), 6.63–8.13(m, 22H)

Mass spectrum (m/z): 583 (M^+)

Process E:

11-(3-Dimethylaminopropylidene)-2-(2-triphenylmethyloxyethyl)-6,11-dihydrodibenz[b,e]oxepin

In this process, 1.2 g of 11-(3-dimethylaminopropyl)-11-hydroxy-2-(2-triphenylmethyloxyethyl)-6,11-dihydrodibenz[b,e]oxepin is dissolved in 50 ml of pyridine. To the solution is dropwise added 0.8 g of phosphorusoxychloride under a nitrogen atmosphere and ice-cooling. After stirring the mixture at room temperature for one hour, the solvent is distilled away under reduced pressure. The residue is extracted with 100 ml of methylene chloride, and washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order. After drying the mixture over anhydrous sodium sulfate, the solvent is distilled away under reduced pressure. The resultant residue is purified by column chromatography on silica gel (eluent: hexane:ethylacetate:triethylamine=10:10:1) to obtain 0.82 g of the desired product as a colorless oily matter.

NMR ($CDCl_3$, δ, ppm): 2.16(s, 6H), 2.30–2.40(m, 4H), 2.79(t, 2H, J=6Hz), 3.24(t, 2H, J=6Hz), 5.97 (t, 1H, J=7Hz), 6.60–7.40(m, 22H), (trans form)

Mass spectrum (m/z): 565 (M^+)

EXAMPLE 3

11-(3-Dimethylaminopropylidene)-2-(2-hydroxyethyl)-6,11-dihydrodibenz[b,e]oxepin (Compound 31)

In this example, 0.92 g of 11-(3-dimethylaminopropylidene)-2-(2-triphenylmethyloxyethyl)-6,11-dihydrodibenz[b,e]oxepin is dissolved in a mixed solvent of 20 ml of water and 20 ml of dioxane. To the solution is added 60 mg of p-toluene sulfonic acid and the mixture is heated at reflux for two hours. The solvent is distilled away under reduced pressure and the residue is extracted with 200 ml of ethylacetate, washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium hydrochloride solution in oder and dried over anhydrous sodium sulfate. The solvent is distilled away under reduced pressure. The resultant residue is purified by column chromatography on silica gel (eluent: ethylacetate triethylamine=10:1) to obtain 0.4 g of the desired product.

Cis form white solid,

Melting point: 100–102° C. (diethylether)

NMR ($CDCl_3$, δ, ppm): 2.32(s, 6H), 2.30–2.70(m, 4H), 2.76(t, 2H, J=6Hz), 3.78(t, 2H, J=6Hz), 5.66(t, 1H, J=7Hz), 6.80–7.40(m, 7H)

Mass spectrum: 323 (M^+)

Trans form white solid,

Melting point: 96°–97° C. (diethylether)

NMR ($CDCl_3$, δ, ppm): 2.21(s, 6H), 2.30–2.70(m, 4H), 2.76(t, 2H, J=6Hz), 3.78(t, 2H, J=6Hz), 6.01(t, 1H, J=7Hz), 6.68–7.40(m, 7H)

Mass spectrum (m/z): 323 (M^+)

EXAMPLE 4

11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenz [b,e]oxepin-2-acetic acid (Compound 20)

In this Example, 2.2 g of 11-(3-dimethylaminopropylidene)-2-(2-hydroxyethyl)-6,11-dihydrodibenz[b,e]oxepin is dissolved in 100 ml of acetone. The Jones reagent is added to the solution until the reaction solution shows an orange color and the mixture is stirred at room temperature for one hour. Sodium bicarbonate is added thereto and an inorganic substance is removed by filtration. The solvent of the filtrate is distilled away under reduced pressure to obtain the desired product. The physicochemical properties of the product coincide with those of the product obtained in Example 35.

EXAMPLE 5

Methyl 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 1)

In this Example, 45 g of (3-dimethylaminopropyl)triphenylphosphonium bromide hydrobromide is suspended in 200 ml of tetrahydrofuran under a nitrogen atmosphere and 82 ml of 1.6N-n-butyl lithium hexane solution is added thereto under ice-cooling. The mixture is stirred under ice-cooling for one hour. To the mixture is dropwise added under ice-cooling a solution obtained by dissolving 10 g of methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate in 200 ml of tetrahydrofuran. After stirring the mixture at room temperature for 2 hours, the mixture is extracted with 800 ml of ethyl acetate. After washing the extract with saturated aqueous sodium chloride solution and drying the extract over anhydrous sodium sulfate, the solvent is distilled away under reduced pressure. The residue is purified by column chromatography on silica gel (eluent: hexane:ethyl acetate:triethylamine = 10:10:1) to obtain 2.0 g of trans form and 5.6 g of cis form of the desired product.

Cis form: NMR ($CDCl_3$, δ, ppm): 2.23(s, 6H), 2.17–2.81(m, 4H), 5.28(bs, 2H), 5.61(t, 1H), 6.80–8.10(m, 7H)

Trans form: NMR ($CDCl_3$, δ, ppm): 2.15(s, 6H), 2.17–2.81(m, 4H), 5.00–5.50(broad, 2H), 6.06 (t, 1H), 6.70–8.10(m, 7H)

EXAMPLE 6

Methyl 11-(3-diethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 4)

The desired product is obtained by substituting (3-diethylaminopropyl)-triphenylphosphonium bromide hydrobromide·½ hydrate for (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in Example 5.

EXAMPLE 7

Methyl 11-(3-pyrrolidinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 6)

The desired product is obtained by substituting (3-pyrrolidinopropyl)-triphenylphosphonium bromide hydrobromide·½ hydrate for (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in Example 5.

EXAMPLE 8

Methyl 11-(4-dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 8)

The desired product is obtained by substituting (4-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide for (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in Example 5.

EXAMPLE 9

Methyl 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 18)

In this example, 48 g of (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide is suspended in 200 ml of tetrahydrofuran under a nitrogen atmosphere and 80 ml of 1.6N-n-butyl lithium hexane solution is added thereto under ice-cooling. The mixture is stirred under ice-cooling for one hour. A solution obtained by dissolving 5.0 g of 11-oxo-6,11-dihydrodibenz [b,e]oxepin-2-acetic acid in 120 ml of tetrahydrofuran is dropwise added under ice-cooling. After stirring the mixture at room temperature for two hours, the solvent is distilled away under reduced pressure. Then, 200 ml of water is added to the residue and the mixture is washed with 200 ml of diethyl ether. The pH of the mixture is adjusted to 1 with aqueous 4N-hydrochloric acid solution and the mixture is washed with diethyl ether.

Then, aqueous 10N-sodium hydrooxide solution is added thereto to adjust the pH of the mixture to 7 and the solvent is distilled away under reduced pressure. The resultant residue is dissolved in 400 ml of methanol and 5 g of p-toluene sulfonic acid is added thereto. After heating the mixture at reflux for two hours, the solvent is distilled away under reduced pressure. The residue is extracted with 300 ml of ethyl acetate, washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order and dried over anhydrous sodium sulfate.

The solvent is distilled away under reduced pressure and the resultant residue is purified by column chromatography on silica gel (eluent: hexane:ethyl acetate:triethylamine = 10:10:1) to obtain 4.0 g of the desired product as a colorless oily matter.

Cis form

NMR ($CDCl_c$, δ, ppm): 2.06–2.67(m, 4H), 2.16(s, 6H), 3.46(s, 2H), 3.58(s, 3H), 5.08(bs, 2H), 5.69 (t, 1H, J = 7Hz), 6.53–7.30(m, 7H)

Trans form

NMR ($CDCl_3$, δ, ppm): 2.06–2.67(m, 4H), 2.16(s, 6H), 3.46(s, 2H), 3.58(s, 3H), 5.08(bs, 2H), 6.06 (t, 1H, J = 7Hz), 6.53–7.30(m, 7H)

EXAMPLE 10

Methyl 11-(4-dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 21)

The desired product is obtained by substituting (4-dimethylaminobutyl)-triphenylphosphonium bromide hydrobromide for (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in Example 9.

EXAMPLE 11

Methyl 11-(3-pyrrolidinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 23)

The desired product is obtained by substituting (3-pyrrolidinopropyl)-triphenylphosphonium bromide hydrobromide. ½ hydrate for (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in Example 9.

EXAMPLE 12

Methyl 3-[11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionate (Compound 27)

The desired product is obtained by substituting 3-(11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-yl)-propionic acid for 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid in Example 9.

EXAMPLE 13

Methyl 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-3-acetate (Compound 29)

The desired product is obtained by substituting 11-oxo-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid for 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid in Example 9.

EXAMPLE 14

Methyl 11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 36)

In this example, 22.0 g of methyl 11-oxo-6.11-dihydrodibenz[b,e]oxepin-2-acetate and 68.7 g of N,N-dimethylethylenediamine are dissolved in 700 ml of dried benzene. To the solution is dropwise added a solution of 17.2 ml of titanium tetrachloride in 40 ml of dried benzene and the mixture is stirred at room temperature overnight. A saturated aqueous sodium bicarbonate solution is added thereto. After removing an insoluble solid by filtration, the filtrate is extracted with 500 ml of ethylacetate, washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order, and dried over anhydrous sodium sulfate. The solvent is distilled away under reduced pressure and the residue is purified by column chromatography on silica gel with ethylacetate/triethylamine (10/1) as an eluent to obtain 13.8 g of the desired product as a colorless oily matter.

NMR ($CDCl_3$, δ, ppm): 2.14(s, 6H), 2.63(t, 2H, J=6.9Hz),
3.51(s, 2H), 3.58(s, 3H), 3.38–3.80
(m, 2H), 5.04(bs, 2H), 6.56–7.60(m, 7H)
IR (neat, cm^{-1}) 2950, 1740, 1630, 1305, 1015
Mass spectrum (m/z): 352 (M^+)

EXAMPLE 15

Methyl-11-(2-diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 34)

The desired product is obtained by substituting methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate for methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetate in Example 14 as a colorless oily matter.

Mass spectrum (m/z): 366 (M^+) for $C_{22}H_{26}O_3N_2$

EXAMPLE 16

Ethyl 11-(2-diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 38)

The desired product is obtained by substituting N,N-diethylethylenediamine for N,N-dimethylethylenediamine in Example 14 as a colorless oily matter.

Mass spectrum (m/z): 380 (M^+) for $C_{23}H_{28}O_3N_2$

EXAMPLE 17

Methyl 11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 40)

The desired product is obtained by substituting N,N-dimethylpropylenediamine for N,N-dimethylethylenediamine in Example 14 as a colorless oily matter.

Mass spectrum (m/z): 366 (M^+) for $C_{22}H_{26}O_3N_2$

EXAMPLE 18

Methyl 3-[11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionate (Compound 42)

The desired product is obtained by substituting 3-(11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-yl)-propionic acid for methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetate in Example 16 as a colorless oily matter.

Mass spectrum (m/z): 394 (M^+) for $C_{24}H_{30}O_3N_2$

EXAMPLE 19

Methyl 2-[11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionate (Compound 44)

The desired product is obtained by substituting 2-(11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-yl)-propionic acid for methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetate in Example 14 as a colorless oily matter.

Mass spectrum (m/z): 366 (M^+) for $C_{22}H_{26}O_3N_2$

EXAMPLE 20

Methyl 11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetate (Compound 46)

The desired product is obtained by substituting 11-oxo-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid for methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetate in Example 14 as a colorless oily matter.

Mass spectrum (m/z): 352 (M^+) for $C_{21}H_{24}O_3N_2$

EXAMPLE 21

Methyl 11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetate (Compound 48)

The desired product is obtained by substituting 11-oxo-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid for 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid in Example 17 as a colorless oily matter.

Mass spectrum (m/z): 366 (M^+) for $C_{22}H_{26}O_3N_2$

EXAMPLE 22

Methyl 11-[2-(4-methylpiperazino)ethylidene]-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 10)

In this example, 1.5 ml of 4-methylpiperazine and 0.37 g of p-formaldehyde are dissolved in 100 ml of tetrachloroethane. To the solution is dropwise added 5 ml of trifluoroacetic acid. After stirring the mixture at 60° C. for 2 hours, a solution obtained by dissolving 1.8 g of methyl 11-methylene-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate in 30 ml of tetrachloroethane is dropwise added thereto and the mixture is stirred at 90° C. for 3 hours.

The mixture is concentrated to dryness under reduced pressure and aqueous 4N-hydrochloric acid solution is added to the residue to adjust the pH to 1. After washing the solution with diethylether, aqueous 10N-sodium hydroxide solution is added thereto to adjust the pH to 13. The mixture is extracted with 200 ml of methylene chloride, washed with saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. The solvent is distilled away under reduced pressure. The residue is purified by column chromatography on silica gel (eluent: hexane:ethyl acetate:triethylamine=5:5:1) to obtain 2.2 g of the desired product as a colorless oily matter.

Cis form: NMR ($CDCl_3$, δ, ppm): 2.24(s, 3H), 2.45(s, 8H), 2.94–3.32(m, 2H), 3.84(s, 3H), 5.22(bs, 2H), 5.85(t, 1H, J=6.8Hz), 6.66–8.07(m, 7H)

Mass spectrum (m/z): 378 (M^+)

Trans form: NMR ($CDCl_3$, δ, ppm): 2.24(s, 3H), 2.45(s, 8H), 2.94–3.32(m, 2H), 3.84(s, 3H), 5.22(bs, 2H), 6.22(t, 1H, J=6.8Hz)

Mass spectrum (m/z): 378 (M^+)

EXAMPLE 23

Methyl 11-(2-morpholinoethylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 12)

The desired product is obtained by substituting morpholine for 4-methylpiperazine in Example 22.

EXAMPLE 24

Methyl 11-(2-thiomorpholinoethylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 14)

The desired product is obtained by substituting thiomorpholine for 4-methylpiperazine in Example 22.

EXAMPLE 25

Methyl 11-(2-pyrrolidinoethylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 16)

The desired product is obtained by substituting pyrrolidine for 4-methylpiperazine in Example 22.

EXAMPLE 26

Methyl 11-(2-piperidinoethylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 17)

The desired product is obtained by substituting piperidine for 4-methylpiperazine in Example 22.

EXAMPLE 27

Methyl 11-[2-(4-methylpiperazino)ethylidene]-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 25)

The desired product is obtained by substituting methyl 11-methylene-6,11-dihydrodibenz[b,e]oxepin-2-acetate for methyl 11-methylene-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate in Example 22.

EXAMPLE 28

11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 3)

In this example, 26.1 g of methyl 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate is dissolved in a mixed solvent of 500 ml of methanol and 30 ml of water and 6.2 g of sodium hydroxide is added thereto. The mixture is heated at reflux for two hours. After allowing the mixture to stand for cooling, aqueous 4N-hydrochloric acid solution is added thereto to adjust the pH to 7 and the mixture is concentrated under reduced pressure. The concentrate is purified by column chromatography on high porous polymer (HP-20) (eluent: water:methanol=1:2) to obtain 25.0 g of the desired product.

Cis form white crystal

Melting point: 162–164° C.

NMR (DMSO-d_6, δ, ppm): 2.28(s, 6H), 2.40–2.70(m, 4H),
5.20–5.40(broad, 2H), 5.72(t, 1H, J=7.0Hz),
6.85–7.90(m, 7H)

IR (KBr disk, cm^{-1}) 3400, 1610, 1370, 1220, 1005

Elemental analysis (%): as $C_{20}H_{21}O_3N \cdot \frac{1}{2} H_2O$

	C	H	N
Found:	73.00	6.67	4.14
Calculated:	72.93	6.63	4.25

Trans form white crystal

Melting point: 242°–244° C.

NMR (DMSO-d_6, δ, ppm) 2.25(s, 6H), 2.40–2.70(m, 4H),
5.20–5.40(broad, 2H), 6.09(t, 1H, J=7.0Hz),
6.78–7.90(m, 7H)

IR (KBr disk, cm^{-1}) 3400, 1610, 1380, 1222, 1010

Elemental analysis (%):

	C	H	N
Found:	74.30	6.60	4.30
Calculated:	74.28	6.55	4.30

EXAMPLES 29–34

11-(3-Diethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 5)

11-(3-Pyrrolidinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 7)

11-(4-Dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 9)

11-[2-(4-Methylpiperazino)ethylidene]-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 11)

11-(2-Morpholinoethylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 13)

11-(2-Thiomorpholinoethylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 15)

These products are obtained by hydrolysis in the same manner as in Example 28

Compound	Melting point (°C.)	Elementary analysis (%) or Mass spectrum			
5	White solid 120–123 (Acetonitrile)	Cis: Trans = 7:3 As $C_{22}H_{25}O_3N$	C	H	N
		Found	75.10	7.11	3.87
		Calculated	75.19	7.17	3.99
7	Colorless amorphous About 150 (Decomposition)	For $C_{22}H_{23}O_3N$ 349 (M^+)			
9	White solid 128–129 (Water)	Cis: Trans = 9:1. dihydrate As $C_{21}H_{23}NO_3.2H_2O$	C	H	N
		Found	67.61	7.03	4.00
		Calculated	67.54	7.29	3.75
11	White solid 150–153 (Water)	Cis: Trans = 1:9. dihydrate As $C_{22}H_{24}NO_3.2H_2O$	C	H	N
		Found	65.98	6.99	6.95
		Calculated	65.98	7.05	7.00
13	White solid 130–133 (Toluene)	Cis: Trans = 1:9 As $C_{21}H_{21}O_4N$	C	H	N
		Found	71.52	6.11	3.81
		Calculated	71.78	6.02	3.99
15	Colorless amorphous About 140	As $C_{21}H_{21}O_3NS$ 367 (M^+)			

EXAMPLE 35

11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 20)

The product is obtained by hydrolysis as in the same manner as in Example 28.

Cis form white crystal

Melting point: 118°–120° C. (Isopropanol)

NMR (DMSO-d_6, δ, ppm): 2.16(s, 6H), 2.30–2.60(m, 4H), 4.04(s, 2H), 5.115(bs, 2H), 5.69(t, 1H, J=7Hz), 6.73–7.40(m, 7H)

Ir (KBr disk, cm^{-1}): 3400, 1580, 1225, 1005

Mass spectrum (m/z): 337 (M^+)

Elementary analysis (%): as $C_{21}H_{23}O_3N$.monohydrate

	C	H	N
Found	70.77	7.36	3.74
Calculated	70.96	7.09	3.94

Trans form white crystal

Melting point: 158°–160° C. (Acetonitrile)

NMR (DMSO-d_6, δ, ppm): 2.05(s, 6H), 2.30–2.60(m, 4H), 4.04(s, 2H), 5.15(bs, 2H), 6.06(t, 1H, J=7Hz), 6.73–7.40(m, 7H)

IR (neat, cm^{-1}): 3380, 1575, 1220, 1005

Mass spectrum (m/z): 337 (M^+)

Elementary analysis (%): as $C_{21}H_{23}O_3N$.monohydrate

	C	H	N
Found	71.06	6.66	3.92

-continued

	C	H	N
Calculated	70.96	7.09	3.94

EXAMPLES 36–39

11-(4-Dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 22)

11-(3-Pyrrolidinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 24)

11-[2-(4-Methylpiperazino)ethylidene]-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 26)

3-[11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionic acid (Compound 28)

These products are obtained by hydrolysis in the same manner as in Example 35. The physicochemical properties are shown in Table 9.

TABLE 9

Compound	Melting point (°C.)	Elementary analysis (%)			
22	White solid 206–209 (Isopropanol)	Cis: Trans = 92:8 as $C_{22}H_{25}O_3N$	C	H	N
		Found	75.20	7.28	4.02
		Calculated	75.19	7.17	3.99
26	White solid 206–209 (Isopropanol)	Cis: Trans = 1:9 as $C_{22}H_{25}O_3N$	C	H	N
		Found	75.19	7.17	3.99
		Calculated	75.15	7.28	3.96

Compound 28

Cis form white crystal

Melting point: 136°–138° C. (Isopropylether)

NMR (DMSO-d_6, δ, ppm): 2.32(m, 2H), 2.38(s, 6H), 2.44–2.56(m, 2H), 2.73(m, 4H), 5.15(bs, 2H), 5.50(m, 1H), 6.7–7.4(m, 7H)

IR (KBr disk, cm^{-1}): 3380, 1645

Mass spectrum (m/z): 351 (M^+)

Elementary analysis (%): as $C_{22}H_{25}NO_3$

	C	H	N
Found	74.83	7.31	3.97
Calculated	75.19	7.17	3.99

Trans form white crystal

Melting point: 148°–149° C. (Acetonitrile)

NMR (DMSO-d_6, δ, ppm): 2.05(s, 6H), 2.24(m, 2H), 2.35(m, 2H), 2.47(t, 2H, J=7.5Hz), 2.72(t, 2H, J=7.5Hz), 4.80–5.50(broad, 2H), 5.99(t, 1H, J=7.1Hz), 6.6–7.5(m, 7H)

IR (KBr disk, cm^{-1}): 3380, 1700

Mass spectrum: 351 (M^+)

Elementary analysis (%): as $C_{22}H_{25}NO_3.1/5$ hydrate

	C	H	N
Found	74.53	7.20	4.32
Calculated	74.42	7.21	3.95

EXAMPLE 40

11-(2-Dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 37)

The desired product is obtained as a 8:92 mixture of cin-form and anti-form by hydrolysis in the same manner as in Example 27.

White crystal

Melting point: 174°–176° C. (as ½ hydrate)

NMR (DMSO-d_6, δ, ppm): 2.07(s, 6H), 2.30–2.80(m, 4H), 3.47(s, 2H), 4.90–5.30(broad, 2H), 6.74–7.62 (m, 7H)

IR (KBr disk, cm^{-1}): 3350, 1575, 1370, 1010

Elementary analysis (%): as $C_{20}H_{22}N_2O_3 \cdot \frac{1}{2}$ hydrate

	C	H	N
Found	69.47	6.77	8.06
Calculated	69.14	6.67	8.06

EXAMPLES 41–47

11-(2-Diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 35)

11-(2-Diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 39)

11-(3-Dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 41)

3-[11-(2-Diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionic acid (Compound 43)

2-[11-(2-Dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionic acid (Compound 45)

11-(2-Dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid (Compound 47)

11-(3-Dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid (Compound 49)

The desired compounds are obtained by hydrolysis in the same manner as in Example 40. The physicochemical properties are shown in Table 10

TABLE 10

Compound	Melting point (°C.)	Elementary analysis (%) or Mass spectrum			
35	White solid 198–200 (Isopropyl ether)	Cin: Anti = 1:1 as $C_{21}H_{24}O_3N_2$	C	H	N
		Found	71.66	6.90	7.82
		Calculated	71.57	6.86	7.95
39	White solid 161–162 (Ethyl acetate)	Anti: 98% as $C_{22}H_{26}O_3N_2$	C	H	N
		Found	72.25	7.24	7.58
		Calculated	72.11	7.15	7.64
41	White solid 171–173 (Isopropanol)	Anti: 97% as $C_{21}H_{24}O_3N_2$	C	H	N
		Found	71.35	6.92	7.69
		Calculated	71.57	6.86	7.95
43	Colorless Oily	as $C_{23}H_{28}O_3N_2$ 380 (M^+)			
45	White solid 132–135 (Water)	Anti > 95% as $C_{21}H_{24}O_3N_2$	C	H	N
		Found	71.39	6.99	7.91
		Calculated	71.57	6.86	7.95
47	White solid 194–195 (Decomposition) (Methanol)	Anti > 95% as $C_{20}H_{22}O_3N_2$	C	H	N
		Found	70.87	6.80	7.93
		Calculated	70.98	6.55	8.28
49	White solid 174–175 (Decomposition) (Isopropanol)	Anti > 95% as $C_{21}H_{24}O_3N_2$	C	H	N
		Found	71.42	7.03	8.06
		Calculated	71.57	6.86	7.95

EXAMPLE 48

Methyl 11-(3-dimethylaminopropyl)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 50) Process A: 11-Hydroxy-2-(4,4-dimethyl-2-oxazoline-2-yl)-6,11-dihydrodibenz[b,e]oxepin

In this process, 2.40 g of 11-oxo-2-(4,4-dimethyl-2-oxazoline-2-yl)-6,11-dihydrodibenz[b,e]oxepin is dissolved in 100 ml of methanol and 0.3 g of sodium borohydride is added thereto. After stirring the mixture at room temperature for 30 minutes, the solvent is distilled away under reduced pressure. The residue is extracted with 200 ml of methylene chloride, washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order, and dried over anhydrous sodium sulfate and the solvent is distilled away under reduced pressure. The residue is recrystallized from toluene to obtain 2.06 g of the desired product as a white solid.

Melting point: 201°–203° C.

Process B: 11-(3-Dimethylaminopropyl)-2-[4,4-dimethyl-2-oxazoline-2-yl)-6,11-dihydrodibenz[b,e]oxepin

In this process, 1.90 g of 11-hydroxy-2-(4,4-dimethyl-2-oxazoline-2-yl)-6,11-dihydrodibenz[b,e]oxepin is dissolved in 30 ml of methylene chloride and 0.7 ml of thionyl chloride is added thereto under ice-cooling. After stirring the mixture at room temperature for one hour, the solvent is distilled away under reduced pressure to obtain a crude product of 11-chloro-2-(4,4-dimethyl-2-oxazoline-2-yl)-6,11-dihydrodibenz[b,e]oxepin. The crude product as such is dissolved in 10 ml of tetrahydrofuran without purification.

To the solution is dropwise added under a nitrogen atmosphere 3-dimethylaminopropyl magnesium chloride obtained in the same manner as in Process C of Example 1 until the raw material is used up. The reaction mixture is extracted with 100 ml of methylene chloride, washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order and dried over anhydrous sodium sulfate, and the solvent is distilled away under reduced pressure. The residue is purified by column chromatography on silica gel (eluent: hexane:ethyl acetate:triethylamine=10:10:1) to obtain 0.06 g of the desired product as a colorless oily matter.

Mass spectrum (m/z): 378 (M^+) for $C_{24}H_{30}O_2N$

Process C: Methyl 11-(3-dimethylaminopropyl)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate

In this process, 60 mg of 11-(3-dimethylaminopropyl)-2-(4,4-dimethyl-2-oxazoline-2-yl)-6,11-dihydrodibenz[b,e]oxepin is dissolved in a mixed solvent of 20 ml of water and 20 ml of dioxane and 10 mg of p-toluenesulfonic acid is added thereto. After heating the

mixture at reflux for 3 hours, the mixture is concentrated under reduced pressure. The concentrate is extracted with 100 ml of ethyl acetate, washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order and dried over anhydrous sodium sulfate, and the solvent is distilled away under reduced pressure. The residue is dissolved in a mixed solution of 30 ml of methanol and 10 ml of aqueous 1N-sodium hydroxide solution and the mixture is heated at reflux for 2 hours. After allowing the mixture to stand for cooling, the pH of the mixture is adjusted to 5.4 with aqueous 4N-hydrochloric acid solution.

The solvent is distilled away under reduced pressure and the residue is redissolved in 50 ml of methanol. After adding 10 mg of p-toluenesulfonic acid thereto, the mixture is heated at reflux for 3 hours and concentrated under reduced pressure. The residue is extracted with 100 ml of ethyl acetate, washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order and dried over anhydrous sodium sulfate and the solvent is distilled away under reduced pressure. The residue is developed on 3 sheets of preparative TLC (20 cm × 20 cm × 0.25 mm) with a mixed solvent (eluent: hexane:ethyl acetate:triethylamine = 10:10:2). The band at R_f = 0.47 is collected, and extracted with methylene chloride and the solvent is distilled away under reduced pressure to obtain 5.3 mg of the desired product as a colorless oily matter.

NMR ($CDCl_3$, δ, ppm): 1.20–1.40(m, 1H), 1.60–1.80 (m, 2H), 2.18(m, 2H), 2.56(s, 6H), 2.74(dd, 2H, J = 6.6Hz and 9.5Hz), 3.90(s, 3H), 5.00 and 5.59 (ABq, 2H, J = 14.2Hz), 6.96–7.88(m, 7H)

Mass spectrum (m/z): 325 (M^+) for $C_{20}H_{23}O_3N$

IR (neat, ν, cm^{-1}): 3400, 1710, 1610, 1110

EXAMPLE 49

½ Fumarate .1/5 hydrate of Compound 3 (Compound 3')

In this example, 3.95 g of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 3) is dissolved in 100 ml of acetone and 1.42 g of fumaric acid is added thereto. The mixture is stirred at room temperature. The deposited crystals are recovered by filtration and recrystallized from isopropanol to obtain 4.15 g of the desired product as a white solid.

Melting point: 253°–254° C.

Isomer purity: Trans form 99% (measured by HPLC)

Elementary analysis (%): as $C_{20}H_{21}NO_3 \cdot \frac{1}{2}C_4H_4 \cdot 1/5 H_2O$

	C	H	N
Found	68.74	6.35	3.61
Calculated	68.63	6.13	3.64

EXAMPLES 50–59

The products identified in Table 11, the physicochemical properties of which are shown in Table 12 are obtained in the same manner as in Example 49.

TABLE 11

Compound No.		
5'	Monofumarate · 1/3 hydrate of Compound 5	(Cis form 99%)
7'	Monofumarate · monohydrate of Compound 7	(Cis form 70%)
11'	Difumarate · 1/2 hydrate of Compound 11	(Trans form 100%)
13'	1/2 Fumarate · 1/2 hydrate of Compound 13	(Trans form 93%)
15'	Monofumarate of Compound 15	(Trans form 100%)
20'	Monofumarate · 3/2 hydrate of Compound 20	(Trans form 95%)
26'	Monofumarate · 2/3 hydrate of Compound 26	(Trans form 88%)
28'	Monofumarate · 1/2 hydrate of Compound 28	(Trans form 63%)
31'	1/2 Fumarate · monohydrate of Compound 31	(Trans form 95%)
33'	Monofumarate of Compound 33	(Cis form 100%)

TABLE 12

Compound	Melting point (°C.)	Elementary analysis (%)			
5'	White solid	as $C_{26}H_{29}O_7N \cdot 1/3H_2O$			
	100		C	H	N
	(Decomposition)	Found	66.03	6.31	2.96
	(Isopropylether)	Calculated	66.14	6.55	3.14
7'	White solid	as $C_{26}H_{27}O_7N \cdot H_2O$			
	vague owing to		C	H	N
	absorption of	Found	64.32	6.11	2.66
	moisture	Calculated	64.59	6.05	2.90
11'	White solid	as $C_{30}H_{32}O_{11}N_2 \cdot 1/2H_2O$			
	266–268		C	H	N
	(Isopropanol)	Found	59.55	5.44	4.53
		Calculated	59.50	5.49	4.63
13'	White solid	as $C_{23}H_{23}O_6N \cdot 1/2H_2O$			
	232–235		C	H	N
	(Decomposition)	Found	66.63	5.83	3.44
	(Isopropanol)	Calculated	66.72	5.85	3.44
15'	White solid	as $C_{25}H_{25}O_7NS$			
	250–254		C	H	N
	(Isopropanol)	Found	64.21	5.59	3.73
		Calculated	64.23	5.39	3.99
20'	White solid	as $C_{25}H_{27}O_7N \cdot 3/2H_2O$			
	135–138		C	H	N
	(Isopropyl	Found	62.58	6.12	2.77
	ether)	Calculated	62.49	6.29	2.91
26'	White solid	as $C_{27}H_{30}O_7N_2 \cdot 2/3H_2O$			
	108–110		C	H	N
	(Isopropanol)	Found	64.15	6.47	5.24
		Calculated	64.02	6.24	5.53
28'	White amorphous	as $C_{26}H_{29}NO_7$			
	vague owing to		C	H	N
	absorption of	Found	66.58	6.61	2.82
	moisture	Calculated	66.80	6.25	3.00
31'	White solid	as $C_{23}H_{27}O_4N \cdot H_2O$			
	vague owing to		C	H	N
	absorption of	Found	65.53	6.81	2.96
	moisture	Calculated	65.39	6.92	3.32
	(Petroleum ether)				
33'	White solid	as $C_{26}H_{31}O_6N$			
	146		C	H	N
	(Acetone)	Found	68.81	7.16	3.22
		Calculated	68.86	6.89	3.09

EXAMPLE 60

Monosodium salt monohydrate of Compound 35 (Compound 35')

In this example, 1.00 g of 11-(2-diethylaminoethyl-)imino-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 35) is dissolved in 100 ml of methanol and 5.5 ml of 28% sodium methoxide methanol solution is added thereto. After stirring the mixture for one hour, the solvent is distilled away under reduced pressure. The residue is triturated by adding isopropylether and is recovered by filtration to obtain 0.98 g of the desired product as a white solid.

Melting point: vague owing to absorption of moisture
Ratio of isomer: Cin:Anti = 1:1
Elementary analysis: as $C_{21}H_{25}O_4N_2Na.H_2O$

	C	H	N
Found	64.23	6.62	7.01
Calculated	64.27	6.68	7.14

EXAMPLES 61 and 62

The same procedures as in Example 60 are repeated to obtain the products identified in Table 13, the physicochemical properties of which are shown in Table 14.

TABLE 13

Compound No.					
43'	Sodium salt of Compound 43	(Anti form 98%)			
45'	Sodium salt monohydrate of Compound 45	(Anti form 99%)			
	Melting point (°C.)	Elementary analysis (%)			
43'	White solid vague owing to	as $C_{23}H_{27}O_3N_2Na$	C	H	N
	absorption of moisture	Found	68.46	7.00	6.88
		Calculated	68.64	6.76	6.96
45'	White solid 140–145	as $C_{21}H_{23}O_3N_2Na.H_2O$	C	H	N
	(Isopropyl ether)	Found	64.11	6.57	6.99
		Calculated	64.27	6.42	7.14

EXAMPLE 63

Tablet

A tablet comprising the following components is prepared in a conventional manner.

Trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid 1/2 fumarate · 1/5 hydrate (Compound 3'):	30 mg
Lactose:	60 mg
Potato starch:	30 mg
Polyvinyl alcohol:	2 mg
Magnesium stearate:	1 mg
Tar pigment:	q.s.

EXAMPLE 64

Powder

A powder comprising the following components is prepared in a conventional manner.

Trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid monofumarate · 3/2 hydrate (Compound 20'):	30 mg
Lactose:	270 mg

EXAMPLE 65

Syrup

A syrup comprising the following components is prepared in a conventional manner.

11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 37):	300 mg
Purified sucrose:	40 g
Methyl p-oxybenzoate:	40 mg
Propyl p-oxybenzoate	10 mg
Strawberry flavor:	0.1 cc
Water is added to the above components until the total valume becomes 100 cc	

EXAMPLE 66

Methyl 11-(3-morpholinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 55)

The desired product is obtained by substituting (3-morpholinopropyl)-triphenylphosphonium bromide hydrobromide for (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in Example 5 as a colorless oily matter.

Mass spectrum (m/z): 379 (M^+) for $C_{23}H_{25}O_4N$

EXAMPLE 67

Methyl 11-(3-thiomorpholinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 57)

The desired product is obtained by substituting (3-thiomorpholinopropyl)-triphenylphosphonium bromide hydrobromide for (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in Example 5 as a colorless oily matter.

Mass spectrum (m/z): 395 (M^+) for $C_{23}H_{25}O_3NS$

EXAMPLE 68

Methyl trans-3-[11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-yl]-acrylate (Compound 59)

The desired product is obtained by substituting trans-3-(11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-yl)-acrylic acid for 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid in Example 9 as a colorless oily matter.

Mass spectrum (m/z): 363 (M^+) for $C_{23}H_{25}O_3N$

EXAMPLE 69

Methyl 11-(3-methylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 61)

The desired product is obtained by substituting (3-methylaminopropyl)-triphenylphosphonium bromide hydrobromide for (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in Example 9 as a colorless oily matter.

Mass spectrum (m/z): 337 (M^+) for $C_{21}H_{23}O_3N$

EXAMPLE 70

Methyl 11-(3-aminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 63)

The desired product is obtained by substituting (3-aminopropyl)-triphenylphosphonium bromide hydrobromide for (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in Example 9 as a colorless oily matter.

Mass spectrum (m/z): 323 (M^+) for $C_{20}H_{21}O_3N$

EXAMPLES 71–75

11-(3-Morpholinopropylidene)-6,11-dihydrodibenz[b,e]-oxepin-2-carboxylic acid (Compound 56)

11-(3-Thiomorpholinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 58)

Trans-3-[11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-yl]-acrylic acid (Compound 60)

11-(3-Methylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 62)

11-(3-Aminopropylidene)-6,11-dihydrodibenz[b,e]-oxepin-2-acetic acid (Compound 64)

The same hydrolysis procedures as in Example 28 are repeated to obtain the desired products, the physicochemical properties of which are shown in Table 15.

TABLE 15

Compound	Melting point (°C.)	Elementary analysis (%) or Mass spectrum			
56	White solid 130–131 (Decomposition)	Cis form 87% as $C_{22}H_{23}O_4N\ C_3H_8O$	C	H	N
	(Isopropanol)	Found	70 65	7 34	3 27
		Calculated	70 57	7.34	3 29
58	White solid 201–205 (Isopropanol)	Cis form 87% 1/2 hydrate as $C_{22}H_{23}O_3NS\ 1/2H_2O$	C	H	N
		Found	67 69	6 03	3 36
		Calculated	67 67	6 20	3 59
60	Colorless oily matter	394 (M^-) for $C_{22}H_{23}O_3N$			
62	White solid	Cis form 100%			

TABLE 15-continued

Compound	Melting point (°C.)	Elementary analysis (%) or Mass spectrum			
	236–238 (Water)	as $C_{20}H_{21}O_3N$	C	H	N
		Found	74.01	6.60	4.01
		Calculated	74 28	6 55	4 33
64	White solid 250 (Decomposition)	Cis form 100% as $C_{19}H_{19}O_3N$	C	H	N
	(Water)	Found	73 57	6.38	4.44
		Calculated	73.77	6.19	4.53

EXAMPLE 76

Cis form of monofumarate of Compound 60 (Compound 60') is obtained in the same manner as in Example 49 as a white solid.

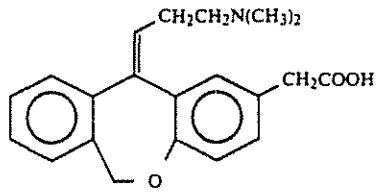
Melting point: 176°–178° C. (Isopropanol)

Elementary analysis (%): as $C_{26}H_{27}O_7N$

	C	H	N
Found	67.09	5 97	2 89
Calculated	67.09	5.85	3.01

What is claimed is:

1. A dibenz[b,e]oxepin compound in cis form having the formula



and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein said salt is selected from the group consisting of acid addition salt, metal salt, ammonium salt, organic amine addition salt, and amino acid addition salt.

3 A pharmaceutical composition comprising a pharmaceutical carrier and as an active ingredient, an effective amount of a dibenz[b,e]oxepin compound defined in claim 1.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,116,863

DATED : May 26, 1992

INVENTOR(S) : ETSUO OSHIMA, ET AL.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

COLUMN 1

Line 64, "$-(CH_2)$hd s" should read -- $-(CH_2)$s--.

COLUMN 2

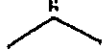
Line 53, "$-(CH_2)$hd m" should read -- $-(CH_2)$m--.

COLUMN 19

Line 48, "Methyl trans-11" should read --Trans-11--.

COLUMN 20

TABLE 2, " $X-(CH_2)_n-Z$ " should read -- $X-(CH_2)_n-Z$ --.

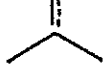


COLUMN 21

TABLE 2-continued, " $X-(CH_2)_n-Z$ " should read -- $X-(CH_2)_n-Z$ --.

COLUMN 22

TABLE 2-continued, " $X-(CH_2)_n-Z$ " should read -- $X-(CH_2)_n-Z$ --.



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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

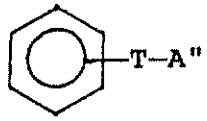
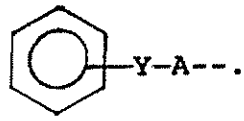
PATENT NO. : 5,116,863

DATED : May 26, 1992

INVENTOR(S) : ETSUO OSHIMA, ET AL. Page 2 of 3

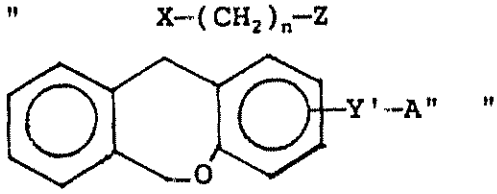
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

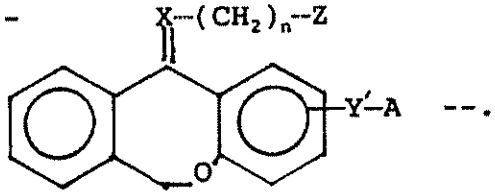
COLUMN 23

TABLE 3, "  should read --  .

Line 30, "21 5.66 6.02 B" should read
--21 5.66 6.02 A--.

COLUMN 24

Lines 26-33, "  "

should read --  .

COLUMN 27

TABLE 5-continued, "300 >100" should read --200 >100--.

--

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,116,863

DATED : May 26, 1992

INVENTOR(S) : ETSUO OSHIMA, ET AL.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

COLUMN 43

Line 44, "5.115(bs," should read --5.15(bs,--.

Signed and Sealed this

Fourteenth Day of September, 1993

Bruce Lehman

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE EXTENDING PATENT TERM UNDER 35 U.S.C. § 156

PATENT NO.	:	5,116,863
ISSUED	:	May 26, 1992
INVENTOR(S)	:	Etsuo Oshima et al.
PATENT OWNER	:	Kyowa Hakko Kogyo Co., Ltd.

This is to certify that there has been presented to the

COMMISSIONER OF PATENTS AND TRADEMARKS

an application under 35 U.S.C. § 156 for an extension of the patent term. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

571 days

from May 26, 2009, the original expiration date of the patent, subject to the provisions of 35 U.S.C. § 41(b), with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).

I have caused the seal of the Patent and Trademark Office to be affixed this 27th day of August 1998.

Bruce A. Lehman
Assistant Secretary of Commerce and
Commissioner of Patents and Trademarks

JS 44
(Rev. 12/96)

CIVIL COVER SHEET

The JS-44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM)

I.(a) PLAINTIFF
Alcon Manufacturing, Ltd., Alcon Laboratories, Inc. and Kyowa Hakko Kogyo Co. Ltd.

(b) COUNTY OF RESIDENCE OF FIRST LISTED PLAINTIFF _____
(EXCEPT IN U.S. PLAINTIFF CASES)

DEFENDANT
Barr Laboratories, Inc.

COUNTY OF RESIDENCE OF FIRST LISTED DEFENDANT _____
(IN U.S. PLAINTIFF CASES ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED

(c) ATTORNEYS (FIRM NAME, ADDRESS, AND TELEPHONE NUMBER)
Frederick L. Cottrell, III
Anne Shea Gaza
Richards, Layton & Finger
One Rodney Square - P.O. Box 551
Wilmington, DE 19899
(302) 651-7700

ATTORNEYS (IF KNOWN)

II. BASIS OF JURISDICTION (PLACE AN X IN ONE BOX ONLY)

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III CITIZENSHIP OF PRINCIPAL PARTIES (PLACE AN "X" IN ONE BOX (For Diversity Cases Only) FOR PLAINTIFF AND ONE BOX FOR DEFENDANT)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

VI. ORIGIN (PLACE AN X IN ONE BOX ONLY)

- ☒ 1 Original Proceeding
- ☐ 2 Removed from State Court
- ☐ 3 Remanded from Appellate Court
- ☐ 4 Reinstated or Reopened
- ☐ 50 Transferred from another district (specify)
- ☐ 6 Multidistrict Litigation
- ☐ 7 Appeal to District Judge from Magistrate Judgment

V. NATURE OF SUIT (PLACE AN X IN ONE BOX ONLY)

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (excl Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholder's Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Eject
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 440 Other Civil Rights

PERSONAL INJURY
- ☐ 362 Personal Injury - Med. Malpractice
- ☐ 365 Personal Injury - Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth In Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence
- Habeas Corpus:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

FORFEITURE/PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 Liquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regs.
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 730 Labor/Mgmt. Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl. Ret. Inc. Security Act

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☒ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS - Third Party 26 USC 7609

OTHER STATUTES

VI. CAUSE OF ACTION (CITE THE U.S. CIVIL STATUTE UNDER WHICH YOU ARE FILING AND WRITE A BRIEF STATEMENT OF CAUSE DO NOT CITE JURISDICTIONAL STATUTES UNLESS DIV
Action under patent laws for declaratory judgment, 35 u.s.c. §1 et seq.

VII. REQUESTED IN COMPLAINT: CHECK IF THIS IS A CLASS ACTION ☐ Under F.R.C.P. 23 DEMAND $ CHECK YES only if demanded in complaint: JURY DEMAND: __YES __NO

VIII. RELATED CASE(S) (See instructions): IF ANY

DATE SIGNATURE OF ATTORNEY OF RECORD
Anne Shea Gaza
November 7, 2007

Anne Shea Gaza

FOR OFFICE USE ONLY
RECEIPT #_____ AMOUNT ____ APPLYING IFP_____ JUDGE _____ MAG JUDGE _____

INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS-44
Authority For Civil Cover Sheet

The JS-44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk

of Court for the purpose of initiating the civil docket sheet. Consequently a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

I. **(a) Plaintiffs - Defendants.** Enter names (last, first, middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency, identify first the agency and then the official, giving both name and title.

(b) County of Residence. For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved.)

(c) Attorneys. Enter firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)".

II. **Jurisdiction.** The basis of jurisdiction is set forth under Rule 8 (a), F.R.C.P., which requires that jurisdictions be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.

United States plaintiff. (1) Jurisdiction is based on 28 U.S.C. 1345 and 1348. Suits by agencies and officers of the United States are included here.

United States defendant. (2) When the plaintiff is suing the United States, its officers or agencies, place an X in this box.

Federal question. (3) This refers to suits under 28 U.S.C. 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.

Diversity of citizenship. (4) This refers to suits under 28 U.S.C. 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below; federal question actions take precedence over diversity cases.)

III. **Residence (citizenship) of Principal Parties.** This section of the JS-44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

IV. **Cause of Action.** Report the civil statute directly related to the cause of action and give a brief description of the cause.

V. **Nature of Suit.** Place an "X" in the appropriate box. If the nature of suit cannot be determined, be sure the cause of action, in Section IV above, is sufficient to enable the deputy clerk or the statistical clerks in the Administrative Office to determine the nature of suit. If the cause fits more than one nature of suit, select the most definitive.

VI. **Origin.** Place an "X" in one of the seven boxes.

Original Proceedings. (1) Cases which originate in the United States district courts.

Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U.S.C., Section 1441. When the petition for removal is granted, check this box.

Remanded from Appellate Court. (3) Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.

Reinstated or Reopened. (4) Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.

Transferred from Another District. (5) For cases transferred under Title 28 U.S.C. Section 1404(a). Do not use this for within district transfers or multidistrict litigation transfers.

Multidistrict Litigation. (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U.S.C. Section 1407. When this box is checked, do not check (5) above.

Appeal to District Judge from Magistrate Judgment. (7) Check this box for an appeal from a magistrate's decision.

VII. **Requested in Complaint.** Class Action. Place an "X" in this box if you are filing a class action under Rule 23, F.R.C.P.

Demand. In this space enter the dollar amount (in thousands of dollars) being demanded or indicate other demand such as a preliminary injunction.

Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

VIII. **Related Cases.** This section of the JS-44 is used to reference relating pending cases if any. If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases.

Date and Attorney Signature. Date and sign the civil cover sheet.
(rev. 07/89)

AO FORM 85 RECEIPT (REV. 9/04)

United States District Court for the District of Delaware

Civil Action No. 07-718

ACKNOWLEDGMENT OF RECEIPT FOR AO FORM 85

NOTICE OF AVAILABILITY OF A UNITED STATES MAGISTRATE JUDGE TO EXERCISE JURISDICTION

I HEREBY ACKNOWLEDGE RECEIPT OF 4 COPIES OF AO FORM 85.

11-702
(Date forms issued)

Shanese L. Hill
(Signature of Party or their Representative)

Shanese L. Hill
(Printed name of Party or their Representative)

Note: Completed receipt will be filed in the Civil Action